DEPARTMENT OF CLINICAL SCIENCES,
DANDERYD HOSPITAL (KI DS)
Karolinska Institutet, Stockholm, Sweden

QUALITY OF LIFE IN MEN WITH INGUINAL HERNIA AND OUTCOME AFTER THREE DIFFERENT MESH TECHNIQUES

Jesper Magnusson

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QUALITY OF LIFE IN MEN WITH INGUINAL HERNIA AND OUTCOME AFTER THREE DIFFERENT MESH TECHNIQUES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Jesper Magnusson

Principal Supervisor:
Professor Anders Thorell
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital (KI DS)

Co-supervisor(s):
Associate professor Jonas Nygren
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital (KI DS)

Opponent:
Associate professor Jan Dalenbäck
University of Gothenburg
Department of Gastrosurgical Research
and Education

Examination Board:
Associate professor Pär Nordin
Umeå University
Department of Surgical and Perioperative
Sciences

Associate professor Gabriel Sandblom
Karolinska Institutet
Department of Clinical Science, Intervention
and Technology

Associate Professor Mikael Ekelund
Lund Univeristy
Department of Clinical Sciences

”Förvänta dig inte något Nobelpris, men för kirurger som sysslar med ljumskbråckskirurgi kan säkert delar av arbetet vara lite intressant”.

Hans L Renck, Professor emeritus i anestesiologi (svärfar)

ABSTRACT

Inguinal hernia repair (IHR) is a very common surgical procedure with approximately 16 000 procedures performed every year in Sweden. Previously, recurrence after IHR was a major concern, but with the introduction of the use of a synthetic mesh, recurrence rates are low today (1-2%). One remaining clinical problem is that some patients develop chronic inguinal pain after IHR, which is associated with impaired quality of life (QoL). The mechanism behind development of chronic pain is not fully understood. New mesh materials and designs are continuously being introduced with the aim of improving results after IHR.

In **paper I**, 309 male patients scheduled for IHR under LA and daycare surgery were randomized to one of three different mesh repairs; Lichtenstein (L), Prolene Hernia System (PHS) and UltraPro Hernia System (UHS). Patients were followed up at 3, 6 and 12 months. Before surgery, physical QoL was impaired compared to the normal population and pain was the most commonly reported symptom. All three methods gave similarly good results regarding perioperative course, recovery, complications, recurrence, chronic groin pain, and improvement in QoL after 12 months. All methods seem to be recommendable for IHR under LA.

In **paper II**, all patients included in paper I were analyzed together and followed up at 12 months. Pain was present in 64 % of all patients and 25 % were asymptomatic. Patients were divided into two groups depending on reported pain from their inguinal hernia (P) or not (N). Before surgery, all included patients (T) and patients with pain (P) reported reduced physical QoL (PCS) compared to the normal population while patients without pain (N) did not. At 12 months after surgery, PCS was increased in all patients and did not differ between groups or compared with controls. However, PCS increased significantly more in group P than in N. The occurrence of preoperative pain is an important factor to consider when scheduling a patient for IHR.

In **paper III,** the patients included in paper I were followed up at 3 years. Twenty-six patients (8%) were lost to follow up. The groups were without differences in any of the studied variables at all follow-up occasions. The number of patients reporting pain decreased during the study period to a total of 7 % and the degree of pain was low. PCS improved similarly in all groups to levels not different from the normal population. Five recurrences were identified, equally distributed between groups. The satisfactory results with all three IHR techniques reported after 12 months were sustained at 3 years postoperatively, further implying that none of these are superior over the other.

In **paper IV,** 3 year follow up of the patients included in paper II is reported. The improvement in PCS seen in group P at 12 months was sustained at 3 years postoperatively whereas PCS in group N did not differ compared to before surgery. These observations demonstrate that the relation between preoperative pain and postoperative improvement in QoL at 12 months is sustained also at long-term follow up (3 years). This underscores further that patients with preoperative pain are those who could be expected to benefit the most from IHR.

In **paper V**, data on 95 808 males undergoing IHR with PHS and L between 1999 and 2014 was collected from the Swedish Hernia Register. Primary IHR with PHS had shorter operation time and fewer complications compared with L. Re-operation due to recurrence after primary IHR with PHS was less common but not more complicated compared with after L, and possible to perform by a laparoscopic approach.

In conclusion, L, PHS and UHS in primary IHR all give satisfactory results that are sustained over a long time. They can all be recommended for males undergoing primary IHR under LA and daycare surgery. Re-operation due to recurrence after PHS is less common compared with L. Recurrent hernia repair is not more complicated after PHS compared with L. The occurrence of preoperative pain is strongly related to preoperative impairment as well as postoperative improvement of physical QoL. Patients with preoperative pain are those who could be expected to benefit the most from IHR.

LIST OF SCIENTIFIC PAPERS

I. **Magnusson J**, Nygren J, Thorell A.
Lichtenstein, prolene hernia system, and UltraPro Hernia System for primary inguinal hernia repair: one-year outcome of a prospective randomized controlled trial. *Hernia. 2012 Jun; 16(3):277-85.*

II. **Magnusson J**, Videhult P, Gustafsson U, Nygren J, Thorell A.
Relationship between preoperative symptoms and improvement of quality of life in patients undergoing elective inguinal herniorrhaphy. *Surgery. 2014 Jan; 155(1):106-13.*

III. **Magnusson J**, Gustafsson U, Nygren J, Thorell A.
UltraPro Hernia System, Prolene Hernia System and Lichtenstein for primary inguinal hernia repair: 3-year outcomes of a prospective randomized controlled trial. *Hernia. 2016 Oct; 20(5):641-8.*

IV. **Magnusson J**, Gustafsson U, Nygren J, Thorell A.
Relationship between preoperative symptoms and improvement in quality of life 3 years after inguinal hernia repair. *Submitted.*

V. **Magnusson J,** Gustafsson U, Nygren J, Thorell A
Incidence and treatment of recurrence after primary inguinal hernia repair with Prolene Hernia System and Lichtenstein. *In manuscript.*

LIST OF ABBREVIATIONS

EHS	European Hernia Society
GA	General anesthesia
HWM	Heavyweight mesh
IHR	Inguinal hernia repair
L	Lichtenstein
LA	Local anesthesia
LWM	Lightweight mesh
MCS	Mental Component Score
N	Patients not reporting pain from their inguinal hernia before surgery
P	Patients reporting pain from their inguinal hernia before surgery
PCS	Physical Component Score
PHS	Prolene Hernia System
QoL	Quality of life
SF-36	Short Form 36
SHR	The Swedish Hernia Register
SIAS	The anterior superior iliac spine
T	Total, all patients taken together
TAPP	Transabdominal preperitoneal repair
TEP	Totally extra peritoneal repair
UHS	UltraPro Hernia System
VAS	Visual Analogue Scale
WW	Watchful waiting

CONTENTS

INTRODUCTION

DEFINITION

An inguinal hernia is a defect in the inguinal area of the abdominal wall which abdominal content (usually preperitoneal fat, intra-abdominal fat or intestines) might bulge through. An inguinal hernia is usually, by itself, a harmless condition but it can be associated with severe morbidity (or even mortality). The only curative treatment is surgery. Inguinal hernia repair (IHR) is one of the most commonly performed surgical procedures in the world. In Sweden, approximately 16 000 patients undergo surgical repair annually [1]. IHR is considered a safe procedure and morbidity rates are low [2], although the risk of postoperative pain should be considered before scheduling patients for surgery. Morbidity rates are, however, significantly increased in case of acute surgery.

INGUINAL ANATOMY

Landmarks

The groin region is related to the following bone structures; the anterior superior iliac spine (SIAS), laterally, the pubic crest (medially) and the symphysis of the pubic bone.
The deep inguinal ring is located midway between SIAS and the pubic symphysis. The superficial inguinal ring is located above and medial to the pubic tubercle. Just below the mid-inguinal point is where the femoral canal is found; below and lateral to the pubic tubercle. From medial to lateral of the canal are the femoral vein, artery and nerve.

The inguinal canal

The inguinal canal could be looked upon as a tunnel. In simple terms, the anterior wall of the tunnel is represented by the external oblique abdominal muscles. Posteriorly, the canal is limited by the internal oblique and transverse abdominal muscles and medially these fuse together constituting the conjoined tendon. Behind the muscles, the transverse fascia and peritoneum are located.
In males, the spermatic cord is running through the inguinal canal and is covered by tissues from the abdominal wall muscles and fascias, created at the deep inguinal ring. In addition to the ilioinguinal

nerve (which runs on the outside of the cord, in the inguinal canal), the spermatic cord contains testicular blood and lymph vessels, vas deferens and the genital branch of the genitofemoral nerve. In females, the canal contains the ilioinguinal nerve and the round ligament. There are three nerves in the inguinal area; the genital branch of the genitofemoral nerve, the iliohypogastric and the ilioinguinal nerve.

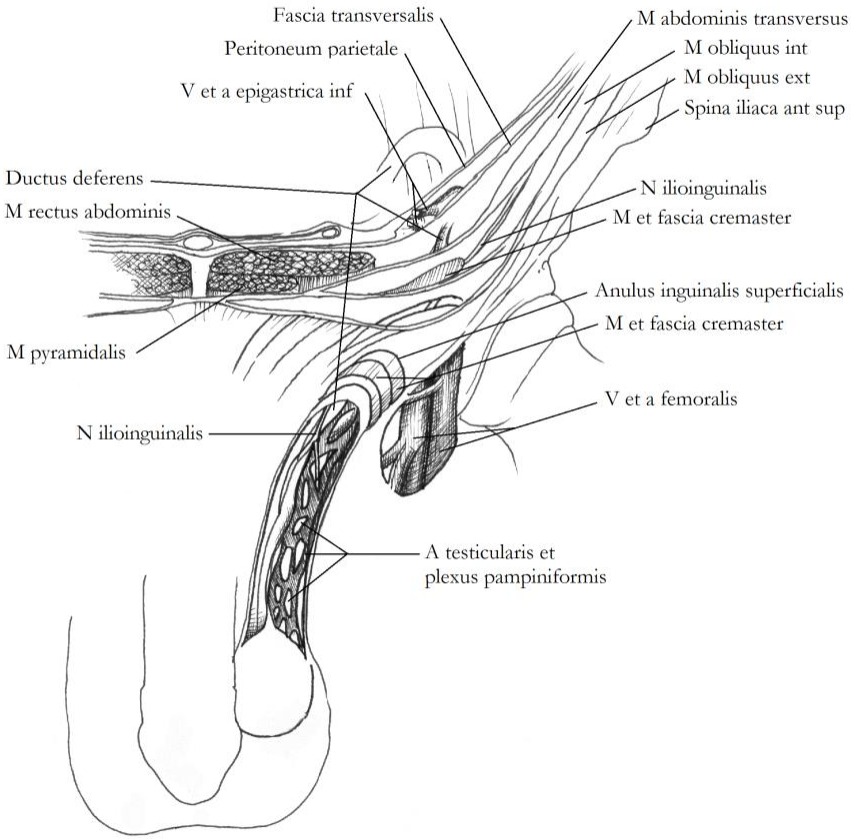

Figure 1. The inguinal canal

CLASSIFICATION

There are four different types of groin hernias: indirect, direct, femoral and combined hernias. They all originate from the fossae of the anterior abdominal wall [3].

Indirect (lateral) hernias	The herniation takes place on the lateral side of the inferior epigastric vessels and passes through the deep ring. The herniation follows the spermatic cord in males and the round ligament in females. A lateral hernia is the most common type and constitutes approximately 54% of all primary hernias[1] .
Direct (medial) hernias	Direct hernias are located on the medial side of the inferior epigastric vessels and the herniation passes "directly" through the floor of the inguinal canal. Medial defects are the second most common type of hernia representing approximately 39% of all groin hernias [1].
Femoral hernias	Femoral hernias are a protrusion of preperitoneal fat or visceral content through the femoral canal.
Combined hernias	A combination of at least two of the hernias mentioned above.

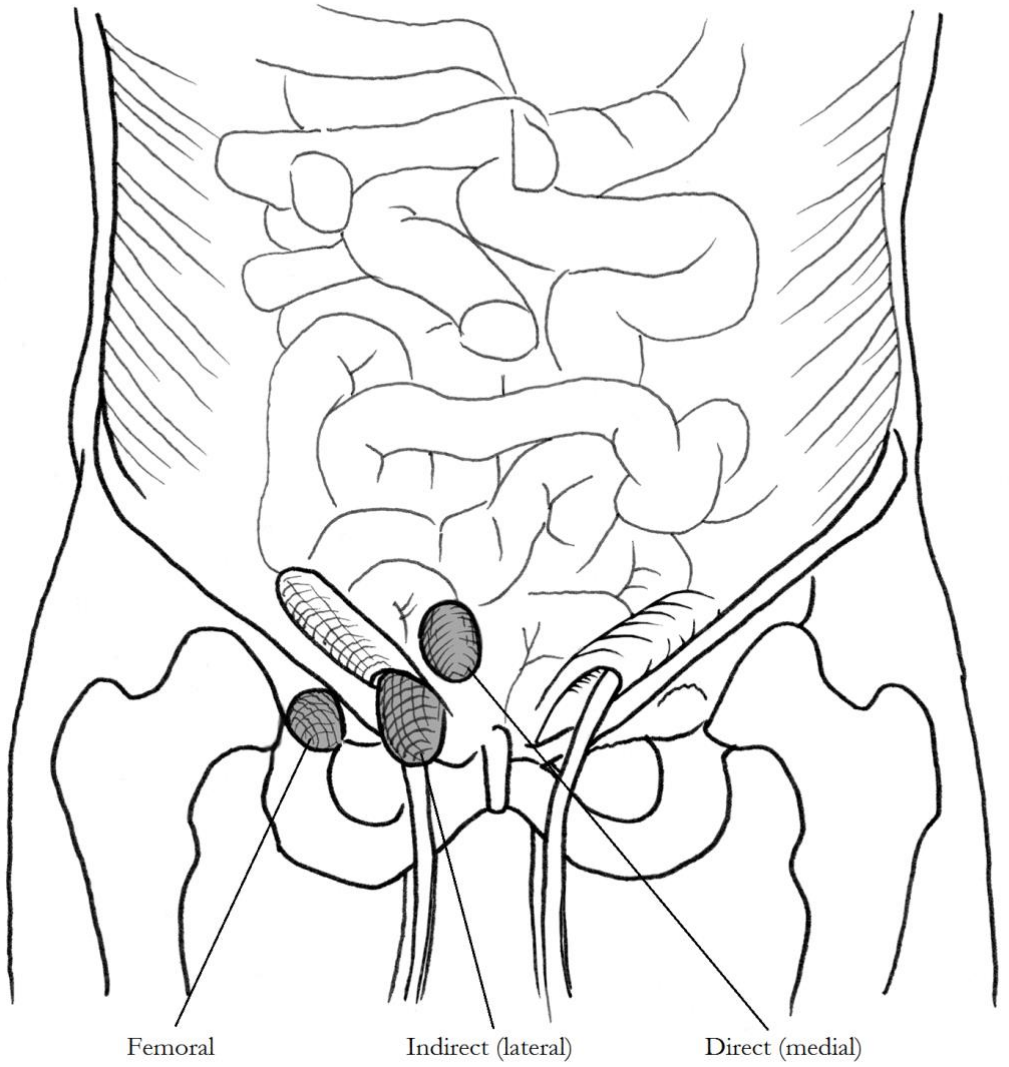

Figure 2. Classification of inguinal hernias.

CLINICAL CLASSIFICATION

Reducible hernia — When the content of the hernia can be reduced back into the abdominal cavity. This is the most common type of inguinal hernia.

Incarcerated / Irreducible hernia When the hernia content cannot be reduced by external pressure. Incarcerated hernias could further be divided into:

Obstructed
When the lumen of the herniated intestine is obstructed.

Strangulated
When the blood supply of the hernia content is obstructed, resulting in ischemia. The lumen of the intestine may be patent or not.

Recurrent hernia A hernia relapse after a previous hernia repair.

EPIDEMIOLOGY

The precise incidence of inguinal hernia is not yet defined. Chang et al estimated a cumulative incidence of inguinal hernia in children (0 – 15 years of age) in Taiwan to 6.6 and 0.7 % in males and females, respectively [4]. Abramson and colleagues investigated the prevalence of patients with non-operated inguinal hernias in men in Jerusalem between 1969-71[5]. They found a prevalence of 18 per 100 in men aged 25 and above. The prevalence was increased with age and the prevalence, including operated hernias, reached 47% in patients aged 75 and above. Ruhl and Everhart made similar findings in the US population with an increasing cumulative incidence of inguinal hernia in men with age, from 7.3 % at age 24–39 years to 22.8 percent at age 60–74 years [6]. In a recently published study from the Netherlands [7], de Goede and colleagues studied a cohort of 14 926 middle aged and elderly men (≥45 years of age), in which a 20-year cumulative incidence of inguinal hernia in 14% was found.

Although the precise incidence and prevalence of inguinal hernia is unknown, it is estimated that over 20 million surgical procedures for inguinal hernia are performed each year worldwide [2, 8]. The lifetime risk from birth of undergoing IHR has been estimated to 27.2 % for males and 2.6% for females [8]. The frequency of surgical treatment differs between countries, for instance 10 per

100 000 in the United Kingdom and 28 per 100 000 in the United States [9]. In low income countries the numbers are much lower.

RISK FACTORS

There are some certain risk factors for developing a primary groin hernia. The presence of a patent processus vaginalis (with a defect in the closing mechanism), aberrant metabolism of collagen and extracellular matrix, sex, ageing, family history, physical exertion, muscle deficiency after abdominal surgery, connective tissue disease, presence of a concomitant hiatal hernia and chronic obstructive pulmonary disorder have all been shown to be associated with an increased risk of developing inguinal hernia [6-8, 10-13]. Obesity has been suggested to be a risk factor [10] but several studies have shown the opposite, with lower incidence of inguinal hernia in obese patients [5, 6, 14].

SYMPTOMS

The most common finding in patients with an inguinal hernia is a bulge in the groin. Sometimes the bulge protrudes or becomes more prominent when the patient is standing up, coughing or lifts heavy objects. Quite often, the bulge will retract spontaneously when the patient is in a supine position.

The most common symptom is various degree of pain [15-18], even though the pain often is mild. Significant pain from the hernia is suggestive of strangulation and might indicate that an emergency operation needs to be performed. Many patients report other symptoms irrespectively if pain is present or not. Such symptoms are often modest and can be described as for example heaviness, tingling, attractions, etc. A large proportion of patients undergoing IHR don't have any symptoms at all [15, 18].

It is not unusual that patients experience discomfort due to the size of the hernia. A large hernia does not have to be painful, but it may serve as a mechanical barrier inhibiting mobility and physical activity.

The definition of symptoms has been developed by the European Hernia Society (EHS) [19]:

Asymptomatic inguinal hernia	Inguinal hernia without pain or discomfort
Minimally Symptomatic hernia	Inguinal hernia with complaints that do not interfere with daily normal activities
Symptomatic inguinal hernia	Inguinal hernia which causes symptoms
Non-reducible inguinal hernia	Inguinal hernia in which the contents of the sac cannot be reduced into the abdominal cavity
Strangulated inguinal hernia	Inguinal hernia which is non-reducible and shows symptoms of strangulation and/or ileus

TREATMENT

The natural course of a non-treated inguinal hernia is unknown because of the difficulty in identifying large groups of patients who have not had their hernias repaired. However, an inguinal hernia will not heal by itself and the only way to cure this condition is by surgery. If surgery is not applicable, e.g. in patients who are not suitable for, or not willing to undergo surgery, the use of a hernia truss can be useful. A truss is designed to maintain the herniated content in place and can only be used in cases of reducible hernias.

INDICATION FOR SURGERY

An operation may be appropriate if there is a need to reduce symptoms, avoid risk of complications or if the condition becomes acute.

Asymptomatic or minimally symptomatic inguinal hernia

Today, watchful waiting (WW) in cases of asymptomatic or minimally symptomatic inguinal hernias is well accepted. The EHS guidelines suggest WW as an acceptable option for men with symptoms in this category [19]. The strategy is based on two RCT's from the US [20] and the UK [21] where patients with minor or no symptoms were randomized to surgery or WW. In summary, the results

after one (US) and two (UK) years suggested that WW is a safe alternative to surgery in presence of minimal or no symptoms from the hernia. Included patients were also followed up after a long time. In the American trial, 2.4% of patients in the WW group were in need of emergency hernia surgery over a 10 year period [22]. The calculated incidence rate of emergency surgery was 0.2 per 100 person-years for all patients but was lower (0.11 per 100 person-years) in patients older than 65 years. Fitzgibbons and colleagues concluded in the US study that WW is a reasonable and safe strategy but inguinal symptoms will likely progress and an operation will be needed eventually. Similar findings were reported in the UK trial where the WW group were followed for in median 7.5 years [23]. In this group, the cumulative incidence of an emergency hernia repair was 2.5%. However, a total of 72% of observed patients underwent surgery during follow-up, in most cases due to development of pain. The conclusion in this study was that surgical repair is recommended for medically fit patients with a painless inguinal hernia because most patients with an asymptomatic inguinal hernia develop symptoms over time. Even if both studies have concluded that symptoms most likely will develop over time, with possible future need of surgery, many centers follow the recommendation of EHS. However, the WW approach has been questioned and it has been suggested that it may expose patients to an increased risk of adverse events [24].

Symptomatic inguinal hernias

Symptomatic hernias cause discomfort and/or pain and are operated on in order to reduce symptoms and/or to prevent future complications [19]. A common opinion is that if an inguinal hernia is affecting activities of daily life, it should be operated.

Non-reducible hernias

Inguinal hernias that cannot be reduced have a higher risk of strangulation [19], which must be considered when the decision regarding surgery is made.

Strangulated inguinal hernia

Strangulated hernia could be a life threatening condition and acute surgical treatment is immediately called for [19].

INGUINAL HERNIA REPAIR

Anesthesia

IHR can be performed under local (LA), regional (spinal, epidural) or general anesthesia (GA). The most appropriate anesthesia must be as easy and safe as possible. Approximately 70% of all IHR in males in Sweden are performed under GA, followed by LA (20 %) and regional anesthesia (10 %) [1]. A majority of all primary IHRs in men are most likely possible to perform under local anesthesia **(**LA). Possibly, the large proportion of GA in IHR is due to the fact that it may be more comfortable for the surgeon with a sleeping patient, and that the administration of LA may be complicated. However, several reports have shown benefits with the use of LA compared to general- or regional anesthesia such as; shorter hospital stay, reduced postoperative pain, lower rates of urinary retention and reduction of unplanned hospital stay due to side effects of anesthesia [25, 26]. In a recently published meta-analysis comparing LA with spinal anesthesia, Prakash and colleagues included ten RCTs with a total of 1 379 patients [27]. They made similar findings with reduced pain, reduced rates of urinary retention and decreased numbers of patients with anesthetic failure with LA compared to spinal anesthesia.

Surgical technique

"The open IHR is the very cornerstone of general surgery" [28].

IHR has been described since the first century A.D [29, 30] and there is some evidence that the Egyptians practiced inguinal hernia surgery even earlier [28]. Many different surgical procedures from around the world and in different time eras have been described. During the 19th century, knowledge and understanding of the anatomy of the inguinal canal increased [28, 30].

Suture repair

Suture repairs are based on the principle that tightening multiple layers of the tissues in the groin will reinforce the weakened area in the inguinal canal, as introduced by Bassini.

The Bassini repair

Eduardo Bassini revolutionized IHR in 1887 with his simple repair, which however required knowledge and understanding of the groin anatomy [31]. Bassini was an Italian surgeon who was

injured by a bayonet in the groin during the Italian war of independence. The injury resulted in a fistula system and for obvious reasons, Bassini got particularly interested in the anatomy of the groin. In the Bassini repair, the inguinal anatomy is recreated by suturing and strengthening of the different layers in the groin. Mortality rates decreased dramatically and when performed correctly, so did recurrence rates. The Bassini repair was introduced outside Italy in 1889, and the technique was so successful that it was quickly adopted by surgeons worldwide, and is still in use today.
Since then, many other techniques have been described, but most of the different procedures were based on the reports from Bassini.

Shouldice

The Shouldice repair has been in use since the 1950's [32] and is considered the gold standard for prosthesis-free surgical treatment of inguinal hernias, in the hands of a dedicated hernia surgeon. In some studies, very good results have been reported, with low recurrence rates (0.7 - 1.7 %) and low incidence of postoperative pain [33, 34].

In clinics where surgeons are not specialized in IHR, various techniques for suture repair have been reported to be associated with high risk of recurrence requiring re-operation in up to 10% [34, 35]. Postoperative pain after surgery is also common after suture repair.

Mesh repair

The next major improvement in IHR was the introduction of prosthetic meshes. Marcy was the first to describe this, recommending kangaroo tendon as mesh material, in year 1887 [28, 36]. Several different repairs with various types of meshes have been described since then. However, it took a century before the big breakthrough for use of meshes in IHR.

The Lichtenstein repair

The open anterior tension free mesh repair, the Lichtenstein repair, was introduced in 1989 [37] and is based on the findings of Bassini but performed with the use of a prosthetic heavy weight polypropylene mesh. The procedure involves reinforcement of the abdominal wall with a flat sheet mesh, which then is integrated with the abdominal wall by ingrowth of fibroblasts. The tension free fixation is used since the mesh will partially shrink when being integrated into the abdominal wall.

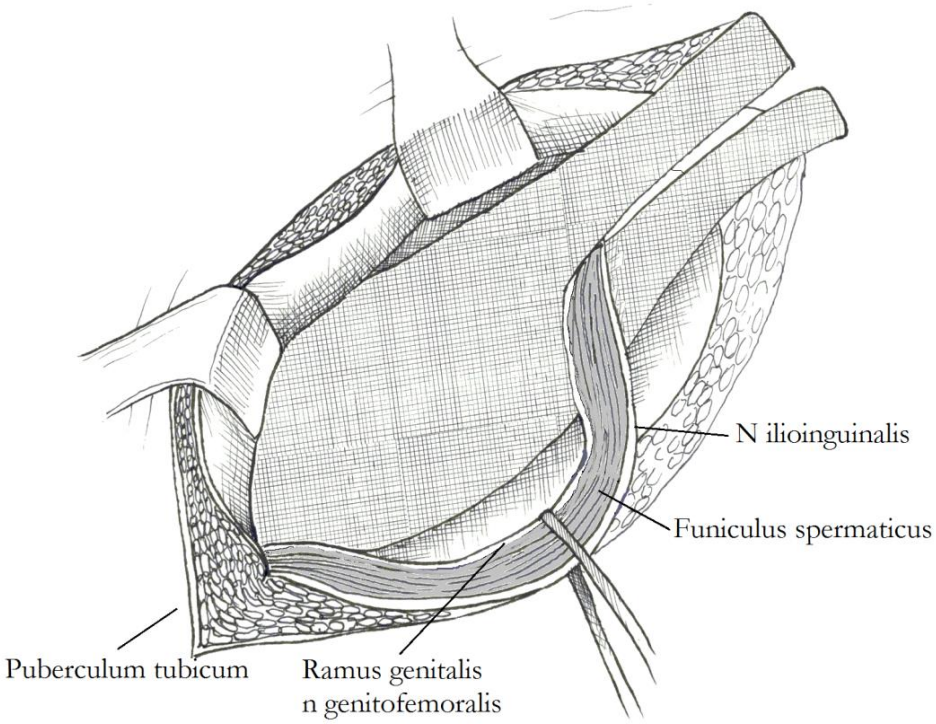

Figure 3. Lichtenstein repair

Since the Lichtenstein repair was introduced and widely accepted, the relapse rate has been reduced dramatically to approximately 1-2% [38]. Moreover, the Lichtenstein technique has been proved to be easy to learn and the outcome is good also in the hands of inexperienced surgeons. This is in contrast to the outcome after suture repair which seems to be more dependent on how experienced the surgeon is. Several reports have verified the superiority of the tension-free mesh technique compared to Shouldice, in terms of recurrence [19, 39-42]. The Lichtenstein repair is now considered the golden standard method of choice in Sweden as well as many other countries in the industrialized world.

Although the Lichtenstein technique still is the predominant method and used in approximately two thirds of all IHR in Sweden, several alternative mesh techniques have been introduced during the last decades.

In most, if not close to all IHR procedures in the industrialized world, some type of mesh-repair is used. Depending on which tension-free method is being used, the mesh is applied in front of, in or behind the weakened area, and is then fixed loosely which allows it to be incorporated into the abdominal wall without inducing tension on surrounding tissue.

Posterior repair

The preperitoneal (posterior) approach of IHR can be dated back to 1876 when it was first presented by Annandale [29]. The posterior approach has been modified and evolved several times since then, but it was Nyhus and colleagues who developed the operation to an established method in the late 1950's [43]. Today, a posterior IHR is usually performed by laparoscopy which is a standard technique in many surgical units. Thus, laparoscopic surgery accounts for approximately 10% of all IHR in Sweden [1] and is the method of choice in recurrent or bilateral hernias as well as for inguinal hernia repair in women [19]. Laparoscopic repair is, however, not discussed further in this thesis.

MESH

The ideal prosthetic mesh for IHR should meet a number of criteria's. It should provide abdominal wall strength with preserved abdominal wall mobility, integrate with the tissue with a minimal foreign body reaction and preferably be without properties causing an extended inflammatory process with the risk of engaging adjacent tissues. If the mesh is too frail, it can burst and cause a relapse and if it is too robust, it can cause discomfort to the patient.

A definition of mechanical mesh properties has been given by the American Society for Testing and Materials. Terminology of textile structures are recommended to be defined in terms of: tensile strength, burst strength, elasticity and stiffness [44]. There are several different types of mesh available, varying in material, construction, elasticity, pore size, tensile strength, surface, degradability, weight and design. Moreover, new mesh designs and materials are continuously being introduced and there are currently more than 160 different meshes for hernia repair available on the market [45].

MESH PHYSIOLOGY – THE FOREIGN BODY REACTION

When put in place in human tissue, the prosthetic mesh and the properties of its materials will induce an inflammatory response and wound healing including a number of different complex processes that are taking place. In an attempt to separate the mesh from surrounding tissues, a fibrotic capsule is created by different types of inflammatory cells that migrate to the mesh. Histologically, the capsule covering an ingrowth mesh contains many different pro- and anti-inflammatory cells such as macrophages, CD3+ lymphocytes, CD8+ T lymphocytes, CD20+ B lymphocytes, neutrophils, mast cells, CD15+ granulocytes and foreign body giant cells. The reaction also modifies the collagen deposition [46]. Moreover, the degree of inflammatory response is related to the amount of fibrosis that will cover the mesh [47].
The fibrotic response is also dependent on the pore size of the mesh. A large pored mesh has been indicated to reduce the inflammatory reaction around the mesh and also minimizing mesh shrinkage [48]. The mesh will eventually reinforce the abdominal wall, partly due to ingrowth of tissues and partly due to inducing an inflammatory scarring of weakened tissues creating a mesh aponeurosis scar tissue (MAST) complex [49, 50].

MESH MATERIAL

Previously used meshes have been consisted by materials such as silver filigree, tantalum sheets, tantalum gauze, stainless steel wire, vitallium and tendons from ox, kangaroo, deer and whales but none of them turned out to be useful [28, 29]. Synthetic material, such as nylon, proved to be a suitable material that could be used as prosthesis. Melick was the first to report this in 1942 [28] and Usher introduced the polyethylene mesh for use in hernia repair in 1958 [51].
Polypropylene (PP) is the most used and most studied prosthetic material in IHR. Other common materials are polyethylene terephthalate (PET), expanded polytetrafluoroethylene (ePTFE) and polyvinylidenefluoride (PVDF). Also, several different absorbable materials are used, e.g. polylactide (PLA), polyglycolic acid (PGA), polycaprolactone (PCL) and polydioxanone (PDO)[44, 52].
Biological meshes are also available but have yet not become an established material for use in IHR. To this date there are only a few RCT's available where biological meshes have been compared with standard synthetic meshes [53].

MESH WEIGHT

The definition of heavyweight (HWM) and lightweight mesh (LWM) varies and is debatable. Pore size is a factor that also should be taken into account besides the actual weight of the mesh [54]. A LWM generally contains less foreign material than a HWM. Coda and colleagues proposed a classification system based on the mesh weight: Ultra-light <35 g/m^2, light 35 - 70 g/m^2, standard 70 - 140 g/m^2 and heavy ≥140 g/m^2 [45]. In reality, a mesh weight of >80g/m^2 is often considered as heavy, and a weight of <50g/m^2 a lightweight [55-57].

Sajid et al published a systematic review and meta-analysis on LWM vs. HWM comprising nine RCT's including a total of 2 310 patients [58]. They concluded that the use of a LWM was not associated with a higher recurrence rate, as indicated in previous studies [59, 60]. Moreover, the use of a LWM was also associated with reduced rates of chronic pain and a trend to reduce the development of other discomforting postoperative symptoms from the groin. The theory behind this will be discussed later in a separate chapter.

MESH DESIGN

New types of mesh designs are constantly being introduced. For use in open inguinal hernia surgery, the most common types of meshes today are different types of flat sheets, mesh plugs and double layer (bi-layer) meshes.

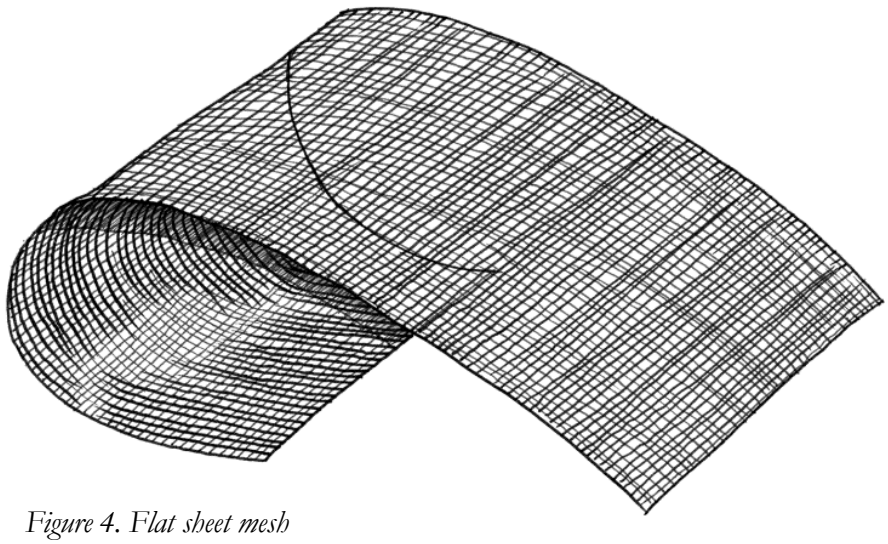

Figure 4. Flat sheet mesh

Flat sheet mesh

The first meshes used in hernia surgery had the design of a flat sheet. Since then, the trend quickly moved forward with a number of variations in design. Flat sheet meshes used today are very similar to a mosquito net and it is still the most commonly used mesh, as in the Lichtenstein repair.

Mesh-plug

Rutkow and Robbins presented an open technique with the use of a cone-shaped mesh plug, placed in the hernia defect in a tension free manner, with or without an onlay mesh on the inguinal floor in 1993 [61]. The mesh plug repair has several times been reported to give results comparable with Lichtenstein, in terms of complications, chronic pain and recurrence [62-65].

Bi-layer mesh

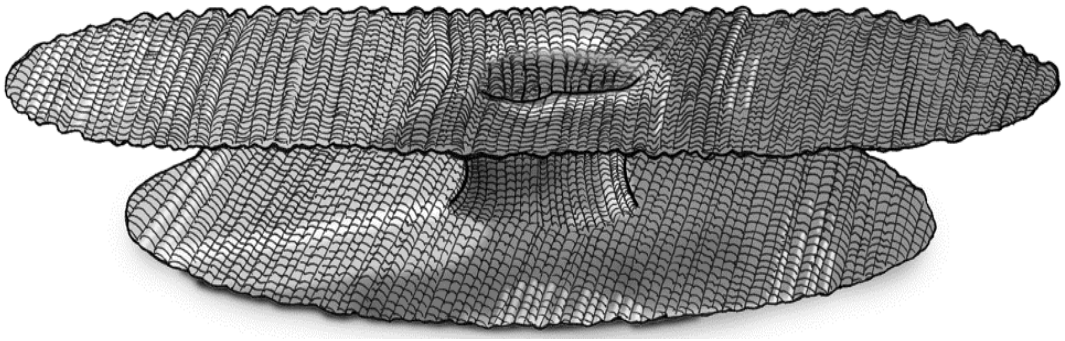

Figure 5. Bilayer mesh

Prolene Hernia System (PHS ®, Ethicon), with a bi-layer polypropylene mesh design and a connector between the layers, has become a commonly used technique and was introduced by Gilbert in 1999 [66]. The bi-layer mesh (BLM) is designed as two separate meshes with a connector between the sheets. In BLM repair, the weakened area in the abdominal wall will be reinforced in three different ways. The posterior sheet of the mesh will reinforce the abdominal wall in the pre-peritoneal space (behind the transverse fascia), the connector levels up the defect in the transverse fascia and the anterior sheet will cover the weakened area with the same principle as in the

Lichtenstein technique. A BLM does not need the same thorough suturing for fixation as the Lichtenstein mesh.

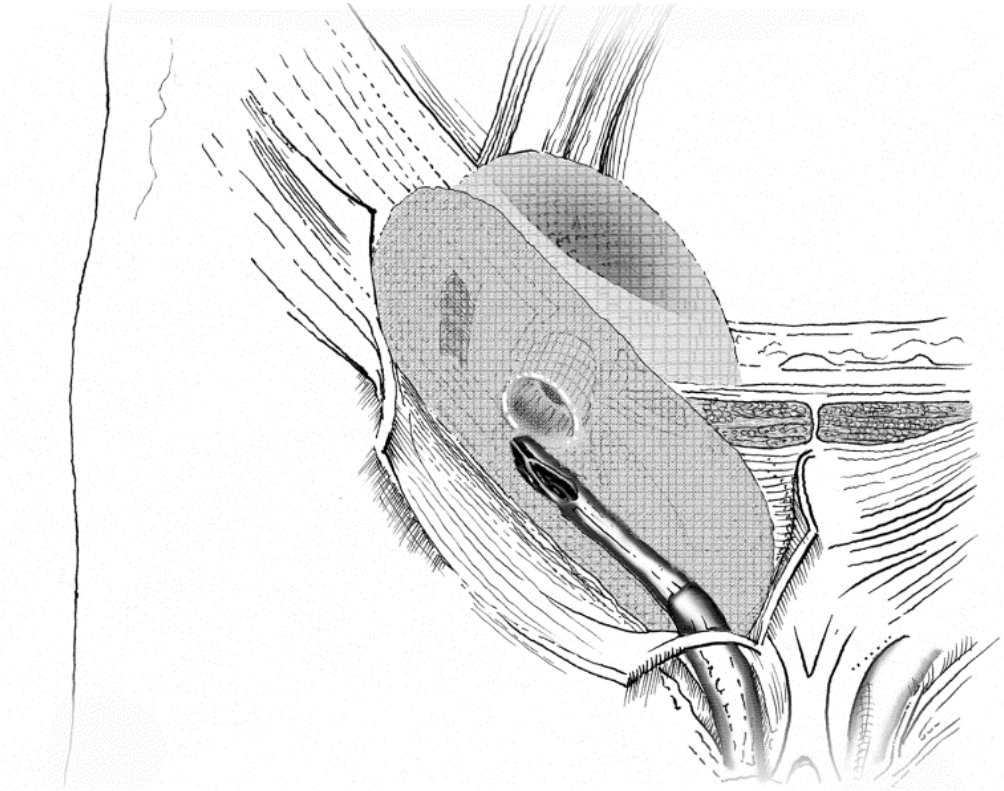

Figure 6. A bi-layer mesh put in place in the inguinal area

PHS has been compared with Lichtenstein in several randomized controlled trials. Kingsnorth et al published one of the first reports on this [67], showing that PHS was associated with a shortened operation time, reduced postoperative pain and a faster recovery to normal activity. Awad et al indicated in a retrospective study of medical charts that PHS might be associated with reduced recurrence rates compared to Lichtenstein [68]. Apart from a shorter operative time, other reports with short and long time follow-up has not been able to show any potential benefits in favor of PHS in terms of recovery, recurrence rates, chronic pain or improvement of quality of life (QoL) [62, 63,

69-73]. In a meta-analysis by Sanjay et al 2012, comparing PHS with Lichtenstein, a total of 1 313 patients were included [72]. They concluded that PHS was associated with an increased risk of peri-operative complications but without detectable differences in terms of short and long-term outcomes. Since recurrence rates are low, irrespectively of which tension-free mesh repair is being used, no published RCT studying PHS have enough power to evaluate this properly. Regarding other parameters, such as mentioned above, the results of surgery appears to be comparable and equally good with the Lichtenstein procedure.

In recent years, a second generation and a further development of the BLM has been introduced; UltraPro Hernia System (UHS ®, Ethicon). The UHS has the same design as PHS, but is made up of lightweight materials with a partially resorbable layer which is placed in the preperitoneal space.

SURGICAL OUTCOME

IHR is usually a straightforward procedure with a rapid recovery to normal everyday activities. A majority of all patients are operated on in a day care setting. Complications are rare and severe morbidity rates following IHR are very low. There is seldom need for sick leave > 1 week.

THE SWEDISH HERNIA REGISTER

The Swedish Hernia Register (SHR) was founded in 1992. Approximately 16 000 IHRs are registered annually on patients aged 15 or older. SHR covers close to 100% of all IHRs performed in Sweden. To this date, the database contains data of more than 240 000 operations. With the use of standardized protocols, data on operations are registered prospectively. Yearly quality checks occur in order to guarantee reliable data. Ten per cent of all participating units are annually visited by five independent external evaluators who check the validity of registered data and check for unregistered IHRs. Data are reported annually to all participating units which then have the possibility to analyze their own results and also to compare it with the rest of the units in the country [1].

COMPLICATIONS TO IHR

Recurrence

Although the incidence of recurrence after IHR is acceptably low, it is still an important outcome factor after surgery. A re-operation due to a recurrent hernia has always been a challenge to surgeons since it is technically more complex than a primary operation. Moreover, outcome after recurrent groin hernia surgery differs from outcome after a primary IHR and is more focused on recurrence rates in addition to chronic pain. In a doctoral thesis published 2014, Sevonius reported that the risk of a re-operation for re-recurrence is twice as high as after a primary intervention [74] . Recurrence rates after Lichtenstein repair has been reported <4 % in the long term [19] and in 0.6-3.3% two to five years after IHR with a BLM (PHS) [62, 63, 68, 69, 75, 76]. Studies with long-term results on UHS are not available at this moment.

Chronic pain

Although recurrence rates have been reduced with the Lichtenstein repair, the technique is not flawless. A problem still concerning hernia surgeons around the world is the development of chronic postoperative groin pain. This unfortunate side effect following IHR is most likely the most important outcome variable today. Also, a state of chronic groin pain has several times been proven linked to reduced QoL [15, 18, 77-82].

The rate of chronic groin pain is usually reported in the range of 10-12% after IHR with the use of a mesh [83-85], but some large studies have shown remarkably high numbers of chronic pain up to 57 - 63% one year after surgery [86, 87]. Previous reports have suggested that the incidence of chronic postoperative groin pain decreases over time [73, 85, 88, 89].

Post herniorraphy pain syndrome

The definition of chronic postoperative pain varies in the literature from "pain of any severity" to "discomfort on exertion" [85]. Many studies use the definition of chronic pain defined by International Association of the Study of Pain (IASP) as "pain persisting beyond the normal tissue healing time assumed to be 3 months" [90]. Later, Alfieri et al defined chronic post herniorraphy neuropathic pain as: "a pain arising as a direct consequence of a nerve lesion or a disease affecting the somatosensory system, in patients who did not have groin pain before their original hernia operation, or, if they did, the post-operative pain differs from the pre-operative pain" [91].

Pathophysiology behind chronic pain

The exact mechanisms underlying chronic groin pain after IHR is not fully understood. Although the origin of the symptoms most likely is multifactorial [92], post herniorraphy pain can in broad terms be divided into neuropathic and nociceptive pain [93-95]. Neuropathic pain is established or caused by a primary lesion or dysfunction of the nervous system [90]. Pinching of the nerves, either by the mesh, fixating materials or scarring around the foreign material has been suggested as possible causes [85, 96, 97]. Neuropathic pain is most often described as a continuous pain but it has also been described to be activated by traction or compression due to tension of the abdominal muscles. Neuropathic pain commonly appears immediately after surgery but can also arise several years after the operation. The diagnosis may be established if the pain is relieved by the administration of LA [90].

The theory behind nociceptive pain is that sensory nerves are activated by local inflammatory mediators around the prosthetic mesh or induced by surgical manipulation [91, 93, 98, 99]. The nerves most at risk for injury are the ilioinguinal, iliohypgastric and the genital branch of the genitofemoral nerve.

LWM was introduced in order to reduce chronic postoperative conditions such as pain, foreign body sensation and/or other inguinal discomfort. Several studies have reported positive findings in terms of reduced chronic pain after LWM compared to HWM, without detectable differences in recurrence rates [56, 58, 100]. A LWM seems to shrink less, cause less inflammation and reduce rates of chronic postoperative pain. The theory behind this is that a reduced amount of foreign material might reduce foreign body reaction and therefore also reduce fibrosis. Physical properties in tissue integration should theoretically also improve since a LWM is more flexible after ingrowth [19, 101]. Since the occurrence and degree of postherniorraphy pain most likely is depending on multiple variables, several studies have focused on other parameters than mesh properties such as method/material used for fixation of the mesh. A mesh can be secured by sutures, tackers, glue or self-gripping micro grips. Fixation of the mesh ad modum Lichtenstein is usually performed with running and interrupted non-absorbable sutures. In Finland, Paajanen compared the use of absorbable vs. non-absorbable sutures in mesh fixation, but could not show any difference in the incidence of pain two years after surgery [102]. Tackers are mainly used in laparoscopic procedures and will not be discussed further in this thesis. The use of glue when securing the mesh has been

studied in several reports. In a meta-analysis conducted by de Goede and colleagues, no detectable differences in chronic pain between glue or suture fixation was seen 1 year after surgery [103]. Self-gripping meshes has gained popularity in recent years and has been shown to significantly reduce operating time but without detectable improvement regarding development of chronic pain [104-106].

However, irrespective the mechanisms, it is clear that occurrence of chronic pain after IHR represents an important area for improvement.

Risk factors for chronic groin pain

There is currently limited knowledge regarding preoperative findings that could indicate an increased risk of developing post herniorraphy pain syndrome. There are several studies that have identified some risk factors that can predict an increased risk of developing chronic pain after IHR such as young age (<40 years), recurrent hernia repair [80, 107], full time employment, presence of preoperative pain, daycare surgery [80], absence of inguinal bulge preoperatively, severe pain after surgery, extended sick-leave [107], female gender [83], open surgery, weight of the mesh and postoperative complications [108, 109]. Certain psychological factors may also influence the development of chronic pain after IHR. Preoperative optimism has been suggested to be a factor that can reduce the development of chronic pain whereas diminished perceived pain control at 1 week after surgery predicted higher pain intensity at 4 months [110].

Pain assessment

There are several tools available for assessment of pain such as the Visual Analogue Scale (VAS) [111], the Numerical Rating Scale (NRS), the Brief Pain Inventory (BPI) and Short Form McGill Pain Questionnaire (SF-MPQ). Beside these, the Inguinal Pain Questionnaire (IPQ) was developed based on the form proposed by Kehlet et al in 2002 [112]. IPQ is an instrument used to evaluate groin pain after IHR and it was validated in 2008 [113]. The form consists of 18 items linked to pain behavior rather than a numerical pain score. The IPQ has become a widely used tool in the assessment of groin pain.

Visual Analogue Scale (VAS)

The 10 graded VAS scale is used as a self-reported assessment for rating of different clinical parameters such as pain or nausea and entities such as asthma or sleeping disorders. The VAS scale is most commonly used for rating of pain. On the scale, 0 represents absence of pain and 10 the worst possible pain. The VAS scale has been found to be reliable and valid for use in a wide range of clinical situations.

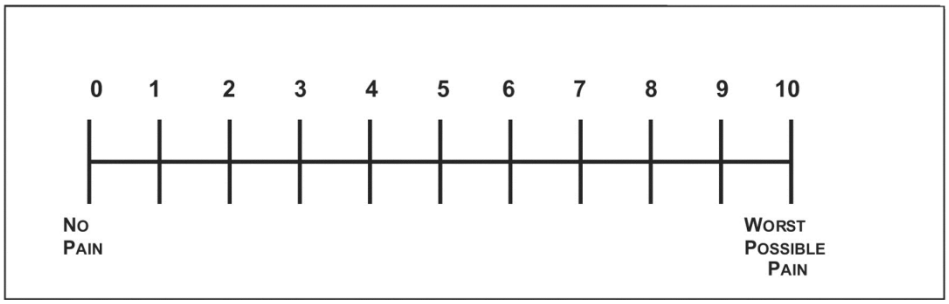

Figure 7. The Visual Analogue Scale.

Treatment of chronic postherniorraphy pain

Not all patients with chronic groin pain are in need of treatment. The few who are severely discomforted from their chronic pain can however be difficult to treat and there are no guidelines available. Some patients are relieved after administration of regional anesthesia or nerve block, but surgical intervention might be needed. Sometimes, a surgical exploration with removal of the mesh and/or neurectomy (selective or multiple) is performed. There are some reports with successful results [114-117] but the condition is considered difficult to treat [118]. Many patients are referred to a pain clinic for other than surgical treatment.

Discomfort/foreign body sensation

The significance of postoperative groin discomfort for the patient's well-being is not precisely established, but most often not considered a major problem. Although the term is used in many studies, it is not uniformly defined. It may be that it is difficult to distinguish between discomfort and pain, since chronic pain often is rated low. Nienhuijs et al published an overview of how postoperative pain has been defined and most often it is not possible to discriminate between pain

and discomfort [85]. Discomfort and other symptoms than pain can be summarized under "other symptoms". A variety of symptoms can be collected in this category; groin discomfort, groin stiffness, foreign body sensation, local hardening, sensory impairment, etc. [58]. Discomforting symptoms several years after surgery has been reported to occur in 5 – 30 % after Lichtenstein and in 11 – 30 % after PHS repair [59, 63, 69, 86, 119]. There are no available data on discomfort in long-term follow up after UHS to this date. Discomfort / foreign body sensation has been shown to diminish with the use of a LWM [120] but it may be without clinical significance.

QUALITY OF LIFE

Quality of life (QoL) can be summarized as the perception of an individual's daily life in aspects of quality regarding their well-being or lack thereof [121]. To evaluate QoL, several factors need to be taken into account such as emotional, social, and physical. In health care, QoL can be evaluated with regards to how the individual's well-being may be affected over time by a disease, disability or disorder.

A validated QoL instrument enables a standardized and thorough way of measuring and comparing the patients' health related QoL (HR-QoL). HR-QoL forms can be generic or specific. Generic HR-QoL is relevant for comparison of different populations in general terms of health. They can be used in all populations while specific HR-QoL are more appropriate when comparing a specific subpopulation or the effect of a particular intervention [122].

There are several different tools for QoL-assessment available such as; Short Form 36 (SF-36), Short Form 12 (SF-12), Quality of Well-Being Index (QWB), Sickness Impact Profile (SIP), Nottingham Health Profile (NHP), Gastrointestinal Quality of Life Index (QLI), EuroQol-5D, Karnofsky Performance Status Scale, 15D and Hernia-Related Quality of Life Survey. Carolinas Comfort Scale (CCS) is a hernia specific QoL-survey for patients undergoing hernia repair with a mesh and was introduced in 2008 [123].

The use of a validated QoL tool can also be used for calculation of economic aspects of surgery. For cost-utility analysis it is possible to use the generic measure of health benefit for calculation of quality-adjusted life years (QALYs). In a Swedish study examining the cost effectiveness of open IHR it was concluded that the return on investment was positive even in patients with minimal or

no symptoms, exceeding all calculated costs [109]. In a British report on cost-effectiveness of hernia surgery it was suggested that the cost for hernia repair is well spent money and that a laparoscopic procedure could be even more cost-effective than open surgery [124].

SF-36

Most studies evaluating QoL in patients undergoing IHR found on PubMed use the validated SF-36 questionnaire [122, 125-128]. The SF-36 is a generic HR-QoL instrument generating a health score in eight different dimensions, for different aspects of health.

In brief, the questionnaire contains 36 questions regarding the patient's physical and mental health the last weeks. The patient scores 4 physical and 4 mental health dimensions, which are transformed into a total domain score between 1- 100, where 100 represent the best possible score. The physical dimensions are: physical function (PF), bodily pain (BP), role-physical (RP) and general health (GH). The mental dimensions are: vitality (V), social functioning (SF), role-emotional (RE) and mental health (MH). All physical and mental dimensions are summarized separately to two domain scores: Physical Component Score (PCS), and Mental Component Score (MCS), respectively. GH, V and SF are included in both PCS and MCS. The SF-36 includes an algorithm to account for non-responders, making the instrument less sensitive to occasional missing values. To evaluate the results, data on all parameters from age- and gender-matched controls are available [126]. SF-36 has been translated into several different languages.

Quality of data

The reliability of a test reflects how the results stand to the "truth", the tool's ability to withstand random results. The level of reliability shows how much the variation can be between the "true values" vs. a measurement error or random. Cronbach´s α is the accepted statistical test used for estimation of the reliability of a psychometric test. A survey can include different questions involving the same output variable. If the questions are measuring the same attribute, the results should correlate and the value of the Cronbach´s α will rise [129].

A reliability of 70% is often quoted as acceptable in questionnaires [126], but only a few instruments have sufficient high reliability at an individual level. In the Swedish standardization of SF-36, all dimensions exceed the critical threshold of 70%. PF and BP exceed 90% while RP and MH are near the upper limit. The high reliability is maintained even when the population's material is divided into

sub-groups. PF and BP have the best reliability in all sub-groups, while SF and RE have the lowest [126].

The validity of a test shows its ability to cover the areas it intends to. To ensure validity in a psychosomatic test, all included dimensions of the questionnaire must be tested in both an internal and external setting. Validity is evaluated on three grounds; *construct, criteria* and *content* validity.

For validity of the construct, test of convergent and discriminant validity are the cornerstones. Test of convergence is performed using different methods in measuring the same variable, receiving similar results. Discriminant validity occurs when a measure of an underlying concept can be distinguished from other concepts. Also, different test groups can be compared (i.e., healthy vs. a specific disease).

Criteria validity can be obtained when sub scores systematically can be related to one or more selected characteristic. Problems may occur if the characteristic is difficult to evaluate. I.e., it is much easier to find robust criteria for physical function than psychosocial. In cases of an unknown criterion, a golden standard, norm data from the population can be very valuable to use for comparison.

Content validity, meaning if the questions are covering the area of interest, is a question of individual valuation which can't be tested statistically. This is a challenge and, therefore, standard rules of general health measures have been designed to optimize the content validity. Validity of content can also be performed by comparing the results with other health surveys. The content of SF-36 has been compared with a selection of several different health related questionnaires. The dimensions in SF-36 correlate moderately to highly in a majority of the different aspects of health [126].
In SF-36, PF has the highest validity in the physical domain and MH in the mental. GH and VT correlate moderately and should be evaluated thereafter.

It is worth mentioning that the various dimensions have different subscales and can't be compared with each other, only with other populations (such as population norms). PF, VT and GH e.g., have 21 levels, MH has 26, while RP only has 5.

In addition to the validity and reliability of a QoL-questionnaire, the instrument's responsiveness (sensitivity to measure changes) is very important for its usefulness as an outcome measure. This was adjusted for by the introduction of a greater number of response options which, on the other hand is causing other difficulties (weighting procedure). It could be considered a weakness when, in general, all types of health are measured in one single dimension. On the other hand, it could also be considered as an advantage, since other dimensions do not cover this particular area of interest. Also, SF-36 can sometimes appear to be long and difficult to answer [128].

AIMS

The overall aim of this thesis is to improve the quality of care, prognosis and QoL for patients with inguinal hernia undergoing open IHR. More specifically, the following questions have been addressed:

1. Is there any difference in 12 months outcome after IHR comparing three different open anterior tension-free mesh repairs with regard to peri-and postoperative course, complications, recurrence, pain and QoL?

2. What are the symptoms in male patients scheduled for IHR in day care surgery under LA?

- Is the hernia causing pain and/or other symptoms, and if so, to what extent?
- How does the inguinal hernia affect QoL?
- Is there any relationship between preoperative symptoms and preoperative QoL?
- What is the effect of IHR on QoL?
- Is there any relationship between preoperative symptoms and postoperative changes in QoL?

3. Is there any difference in long term (3 years) outcome after IHR comparing three different tension-free mesh repairs with regard to QoL, chronic pain, recurrence or other discomforting symptoms?

4. What is the long-term effect of IHR on QoL, pain and/or other symptoms from the hernia?

Is there a relation between preoperative symptoms and the long-term effect of IHR on QoL?

5. Focusing on recurrence after primary IHR with a BLM:

- What is the re-operation rate due to recurrence after a primary IHR with a BLM?
- Which surgical procedure is used in re-operation due to recurrence?
- Is a re-operation due to recurrence more complicated compared to re-operation after primary IHR with Lichtenstein?
    - Is there any difference in operation time?
    - Are the complication rates similar?

METHODS

OVERVIEW OF PAPERS

Study	Design	Subjects
Study 1	Randomized controlled trial	309 male patients
Study 2	Cohort study	309 male patients
Study 3	Randomized controlled trial	309 male patients
Study 4	Cohort study	309 male patients
Study 5	Register-based national cohort study	95 808 male patients

PATIENTS

Paper I-IV

The patients in paper I-IV in this thesis were included in a randomized controlled trial comparing three different techniques for open IHR. Between 1st of November 2006 and 31th of January 2009, all male patients between 18-75 years of age scheduled for primary open unilateral IHR in day care surgery under LA at the clinic were considered for participation in the study. Patients with bilateral hernias, recurrence, ongoing substance abuse, impaired cognitive function, limited mobility or capacity to communicate in Swedish were not eligible. According to the local hernia management program of the clinic, patients with an asymptomatic hernia or with minor symptoms were, in general, recommended not to undergo surgery.

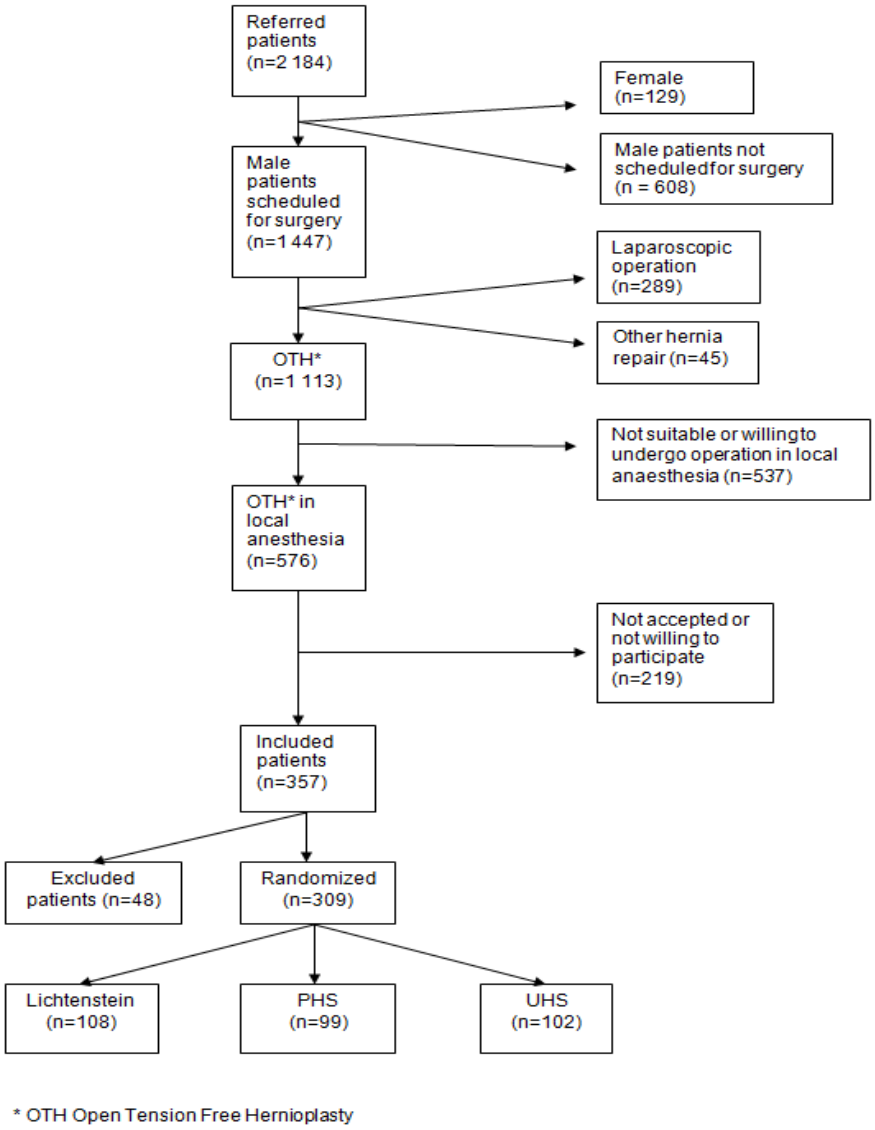

Figure 8. Consort diagram.

Paper V

Paper V is a register-based national cohort study with data retrieved from the national Swedish Hernia Register (SHR) [1]. Data on all operations on males during 1999-2014 where a BLM or Lichtenstein was used in primary IHR were collected. In addition, data on surgery due to recurrence after IHR with a BLM or Lichtenstein has been analyzed and compared.

ETHICS

The study (KCTR-CT20090022) was approved by the regional ethics committee (Dnr 2006/672-31/4) and all participants gave their written informed consent after being informed orally as well as in writing about the nature and the purpose of the study.
The register-based study was approved by the regional ethics committee (Dnr 2015/351-31/1). Each study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All studies were conducted at Ersta hospital, Stockholm, Sweden.

POWER AND STATISTICAL ANALYSIS

Paper I and III

For Paper I and III, the following power calculation was used. Using incidence of groin pain 12 months after surgery as primary end point with an expected rate of 12% in the Lichtenstein group, power calculation revealed that approximately 100 patients per treatment group were needed to include in order to detect a reduction by 8 percent units (to 4%) in any of the two other groups with a significance level of 0.05 and a power of 80%.
For comparisons within and between groups, Chi-square test, Kruskal-Wallis test, Friedman ANOVA, Wilcoxons matched pairs test and student's t-test were used, when appropriate. A p-value of <0.05 was considered statistically significant. All data were analyzed using STATISTICA® (StatSoft Scandinavia AB, version 10 for Windows) or STATA® (version 10.0 for Windows).

Paper II and IV

For Paper II and IV, the sample size of the study was based on the power calculation for the randomized study comparing three different meshes (see above). Since we were not aware of any robust data reporting changes in QoL 12 months after open inguinal repair, no specific power calculation was performed for this study. However we assumed that 300 patients should be a sufficient number of patients in order to address our hypothesis with changes in QoL as primary and pain according to VAS as secondary endpoints.

For univariate comparison between and within groups, the Mann- Whitney U test, the Wilcoxon test, Chi-square test, or Student two-tailed paired or unpaired test were used, when appropriate. Differences over time were tested with two-way ANOVA and Chi-square test. Multiple linear regression was used for adjusted comparisons of PCS and MCS pre- and postoperatively. The adjustment variables were: age, body mass index (BMI), type of mesh used, duration of the operation, and concomitant disease. A p-value of <0.05 was considered statistically significant. All data were analyzed using STATISTICA® (StatSoft Scandinavia AB, version 10 for Windows) or STATA® (version 10.0 for Windows).

Paper V

For paper V, no power calculation was performed since there is no reliable robust data available on recurrence after IHR with a BLM. To circumvent this, we used all data available in one of the largest hernia registers in the world (SHR). For univariate comparison between and within groups, Chi-square test, Wilcoxon test or Mann-Whitney U-test were used, when appropriate. Multiple logistic regression analysis was used for adjusted comparisons of recurrence rates and complications. The adjustment variables were: age, ASA-class, type of hernia and size of the hernia defect. Analysis was undertaken using Statistica® version 13 (StatSoft, Dell Software, USA) for Windows and STATA (version 13 for Windows, College Station, TX). $P<0.05$ was considered statistical significant.

STUDY DESIGN AND PROTOCOLS

Paper I

Study design

The study was designed as a randomized, double blinded, single center study with patients randomly allocated to one of three different open inguinal mesh repairs; Lichtenstein (L), PHS (P) or UHS (U). Patients were randomized on the day of surgery using numbered and sealed envelopes in blocks of 9 each, with computer-generated information on allocation. The envelopes were unsealed after administration of LA with the patient on the operation table ready for surgical intervention. Patients were informed by letter on which mesh was used after the study was completed. Operation journals were closed during the 36 month study period in order to make follow-up investigators and surgeons blinded to group allocation.

Protocols

Included patients were asked to fill out two different protocols.

First, a hernia-specific protocol was used. In this, it was documented whether the hernia was painful at rest and/or during motion and the degree of any pain was quantified with the use of VAS. A VAS score ≥3 was considered as "substantial pain". Also, in this protocol any other discomfort from the groin was reported and described with the patient´s own words.

Secondly, QoL assessment was carried out by the use of the Swedish version of SF-36 with data on all parameters from age- and gender-matched controls randomly selected from the Swedish population during 1998-1999 available. For the current study 3 857 subjects matched for age (18-75 yr.) and gender (male) were used.

Follow-up

From day 1 – 14, patients were asked to estimate postoperative pain, at rest and in motion, daily by the use of a 0-10 graded VAS-scale as well as to document the amount of analgesics used.

At 3, 6 and 12 months after surgery, the two questionnaires described above were filled out by all patients. Patients reporting any symptom suggestive of a complication were contacted by a study nurse who offered and recommended a visit to a surgeon who was blinded to group allocation. The

same recommendation was also given to any patient calling spontaneously during the follow-up time and complaining over such symptoms.

Paper II

Study design

The same cohort of 309 male patients as included in Paper I was analyzed in this study. Included patients were divided into two groups depending on whether they indicated preoperative inguinal pain (P) or not (N). The study protocol, as described for Paper I, included randomization between IHR using one out of three different meshes. Data on comparisons between groups randomized to different meshes are not presented in Paper II. However, all results are adjusted for surgical technique used, as well as for other possible confounders (see above).

Protocols

Included patients were asked to fill out two different protocols preoperatively and at one year after surgery, as described for Paper I. In addition, several specific questions from the physical dimensions of SF-36 were selected and processed separately. The questions were related to restrictions in specific tasks in daily life and capacity to perform regular work. The alternative answers for such restriction were "none", "mild", "moderate", or "severe", which were dichotomized into either "none/mild" or "moderate/severe".

Follow-up

At three, six and twelve months after surgery, the two questionnaires were sent to and filled out by all patients. Patients reporting any symptom suggestive of a complication or recurrence were contacted by a study nurse who offered and recommended a visit to a surgeon who was blinded to group allocation. The same recommendation was also given to any patient calling spontaneously during the follow-up time and complaining over such symptoms. Patients who did not answer were contacted by a nurse by phone. If the patient still didn't respond, this was registered as "missing data".

Paper III

The same study design and protocols as in Paper I were used.

Follow-up

At 3, 6, 12, 24 and 36 months after surgery, the two questionnaires described above were filled out by all patients. For further details please see Paper I above.

Paper IV

The same study design and protocols as in Paper II were used.

Follow-up

At 3, 6, 12, 24 and 36 months after surgery, the two questionnaires described above were filled out by all patients. For further details please see Paper II above.

Paper V

Study design

The study was designed as a register-based national cohort study. Data was retrieved from SHR. Male patients who were 15 years or older at the time of surgery and underwent a primary IHR with PHS or Lichtenstein between January 1st 1999 – December 31st 2014 were included. In addition, data on re-operations due to recurrence after a primary IHR with any of the two techniques during the same time period was also collected.

Protocols

Data collected regarding primary IHR with PHS or Lichtenstein:

- Age at the time of surgery
- Operation time
- Type of hernia
- The size of the defect

- Management of the hernia sac
- Number and type of postoperative complications

Data collected regarding re-operation due to recurrence after a primary IHR with a PHS or Lichtenstein:

- Age at the time of re-operation
- Operation time
- Type of recurrent hernia
- Surgical method used
- Number and type of postoperative complications

RESULTS

PAPER I AND III

Three hundred and nine male patients scheduled for primary IHR under LA in a daycare setting were randomized to one of three groups at the day of surgery (Lichtenstein (L), PHS (P) or UHS (U)). The three groups were well matched regarding age, BMI and physical workload during work and leisure activities, Table 1.

	Lichtenstein	**PHS**	**UHS**
n	109	99	102
Age (yr), median (IQR)	60 (49-64)	58 (48-63)	59 (46-66)
BMI (kg/m2), median (IQR)	24.6 (23.0-26.0)	24.8 (23.2-26.3)	25 (23.0-26.5)
Occupation			
- Office/light workload, n (%)	50 (46)	42 (42)	45 (44)
-Student/retired/unemployed, n (%)	31 (28)	20 (20)	32 (31)
- Heavy work, n (%)	28 (26)	37 (37)	25 (25)
Leisure activities			
- Light	69 (63)	61 (62)	60 (59)
- Heavy	39 (36)	36 (36)	42 (41)
- Missing	1 (1)	2 (2)	0 (0)

Table 1. Baseline characteristics, p=ns, Kruskal Wallis test.

Patients were followed up for a total of 36 months. Follow-up occasions and frequencies are shown in Figure 9. At 36 months, 26 patients (8 %) were lost to follow-up.

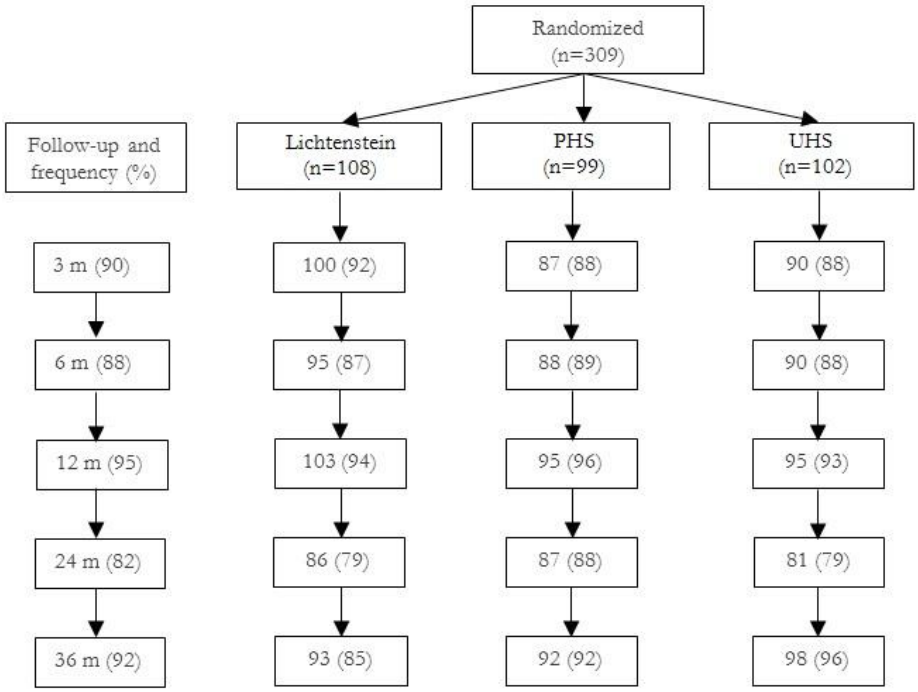

Figure 9. Follow up.

Complications

There were no differences between groups regarding intra- and postoperative data such as operation time, amount of local anesthesia used, blood loss, time until discharge, recovery and return to activities of daily life and workload. For employed patients, there were no differences in sick leave between groups. Intra- and immediate postoperative complications were seen in three patients. Two patients were converted to general anesthesia; one patient in group L due to inadequate pain relief and one in group U due to vomiting and need of securing the respiratory tract. Also, one patient in group L was re-operated on due to bleeding, a procedure performed under LA. During the first 30 days after surgery, a total of 35 patients reported symptoms that motivated a clinical examination by a surgeon blinded for group allocation. A complication was found in 22 patients of which most (86 %) were hematoma and wound infection. The number of early complications was equally distributed between the groups. During the rest of the study period, between 30 d and 36 months, a total of 131 patients (42 %) were examined by a surgeon blinded for group allocation. Most patients had an inguinal bulge and in a vast majority of cases (86%) this was considered as normal postoperative findings. A total of five (1.6 %) recurrences were diagnosed. Three of these were found within the

first 12 months (one in each group), between 12 and 24 months one (in group L) and one between 24 and 36 months postoperatively (in U).

	Lichtenstein	**PHS**	**UHS**	**Tot**
Pre-op n (%)	108	99	102	309
Pain n (%)	67 (62)	65 (66)	65 (64)	197 (64)
VAS at rest	1 (0.3-2.2)	0.8 (0.3-2.8)	0.8 (0.4-2.5)	
VAS in motion	3 (1.5–5.4)	3.5 (1.8–5.6)	3.4 (2.2–5.6)	
VAS>3 n (%)	37 (34)	38 (38)	38 (37)	113 (37)
12 m n (%)	103 (94)	95 (96)	95 (93)	293 (95)
Pain n (%)	15 (15)	12 (12)	13 (13)	40 (13)*
VAS at rest	0.2 (0-0.6)	0.2 (0-1.9)	1 (0.2-2.5)	
VAS in motion	0.5 (0.2-3.1)	0.5 (0.3-3)	2.3 (0.7-2.9)	
VAS>3 n (%)	4 (4)	3 (3)	3 (3)	10 (3)*
Satisfied n (%)	98 (95)	86 (91)	87 (92)	271 (92)
24 m n (%)	86 (79)	87 (88)	81 (79)	254 (82)
Pain n (%)	7 (8)	12 (14)	12 (15)	31 (12)*
VAS at rest	0.3 (0.1-0.7)	0.3 (0.1-0.8)	0.8 (0.4-1.3)	
VAS in motion	0.7 (0.4-1.5)	0.9 (0.4-2.1)	1.2 (0.4-2.6)	
VAS>3 n (%)	1 (1)	2 (2)	1 (1)	4 (1.6)*
Satisfied n (%)	80 (93)	84 (97)	78 (96)	242 (95)
36 m n (%)	93 (85)	92 (92)	98 (96)	283 (92)
Pain n (%)	6 (6)	6 (7)	9 (9)	21 (7) †
VAS at rest	0.4 (0.2-1.7)	0.2 (0.1-2.3)	1.6 (0.7-4.6)	
VAS in motion	0.6 (0.2-1.7)	0.4 (0.2-2.3)	2 (1.4-3)	
VAS >3 n (%)	1 (1)	1 (1)	2 (2)	4 (1.4)*
Satisfied n (%)	91 (98)	83 (90)	85 (87)	259 (96)

*Table 2. VAS. Pain according to VAS pre-operatively and 12, 24 and 36 months after surgery. Values are given as median and interquartile range. * p>0.05 vs preoperatively, † p>0.05 vs 12 months, p = ns between groups.*

Pain and discomfort

Before surgery, two out of three patients reported inguinal pain, equally distributed between groups, Table 2. The degree of pain as rated by VAS was similar as well. The number of patients reporting pain decreased similarly in all groups during the first two weeks after surgery and remained at similar levels during the entire follow-up period. During the first year, incidence of pain decreased overall by 80% (from 197 to 40), without differences between groups. Further, the number of patients reporting pain decreased to 31 (12 %) and 21 (7 %) at 24 and 36 months, respectively. Pain scores according to VAS was low compared to preoperatively and remained at similar levels in all groups at all follow-up points. Substantial pain (VAS≥3) was present in more than one third of all patients in the preoperative situation, equally distributed between the groups. Patients with substantial pain were significantly reduced from 113 to 10 patients at 12 months and lowered to a total of four patients by 24 and 36 months (1.4 %).

In the analysis for paper III, discomforting symptoms except pain was a common complaint before surgery, present in 70 patients and equally distributed between the groups. The number with such symptoms declined during the study period to a total of 61, 51 and 46 patients after 12, 24 and 36 months respectively. This reduction was non-significant and without differences between the groups. Foreign body sensation was the most commonly reported discomforting symptom at 36 months (6.7% of all patients), Table 3.

	L	**PHS**	**UHS**	**Tot**
n (%)	93 (85)	92 (92)	98 (96)	283 (92)
Pain	6	6	9	21 (7)
Recurrence	2	1	2	5 (1.8)
Foreign body sensation	7	9	3	19 (6.7)
Other discomfort	10	8	9	27 (9.5)
Satisfied n (%)	91 (99)	83 (94)	85 (93)	259 (92)

Table 3. Findings 36 months postoperatively.

QoL

QoL assessment was performed with the use of the Swedish version of SF-36. Preoperatively, PCS was significantly reduced compared to matched controls from the normal population, similarly in all groups. Physical QoL increased to levels not different compared to matched controls after three months and were unchanged during the rest of the entire follow-up period. No differences in PCS were noted between the three groups at any time point, Figure 10. The mental component score of SF-36 (MCS) was not affected before or after surgical intervention. MCS did not change in any of the groups and scores did not differ within or between groups or compared to matched controls at any time point.

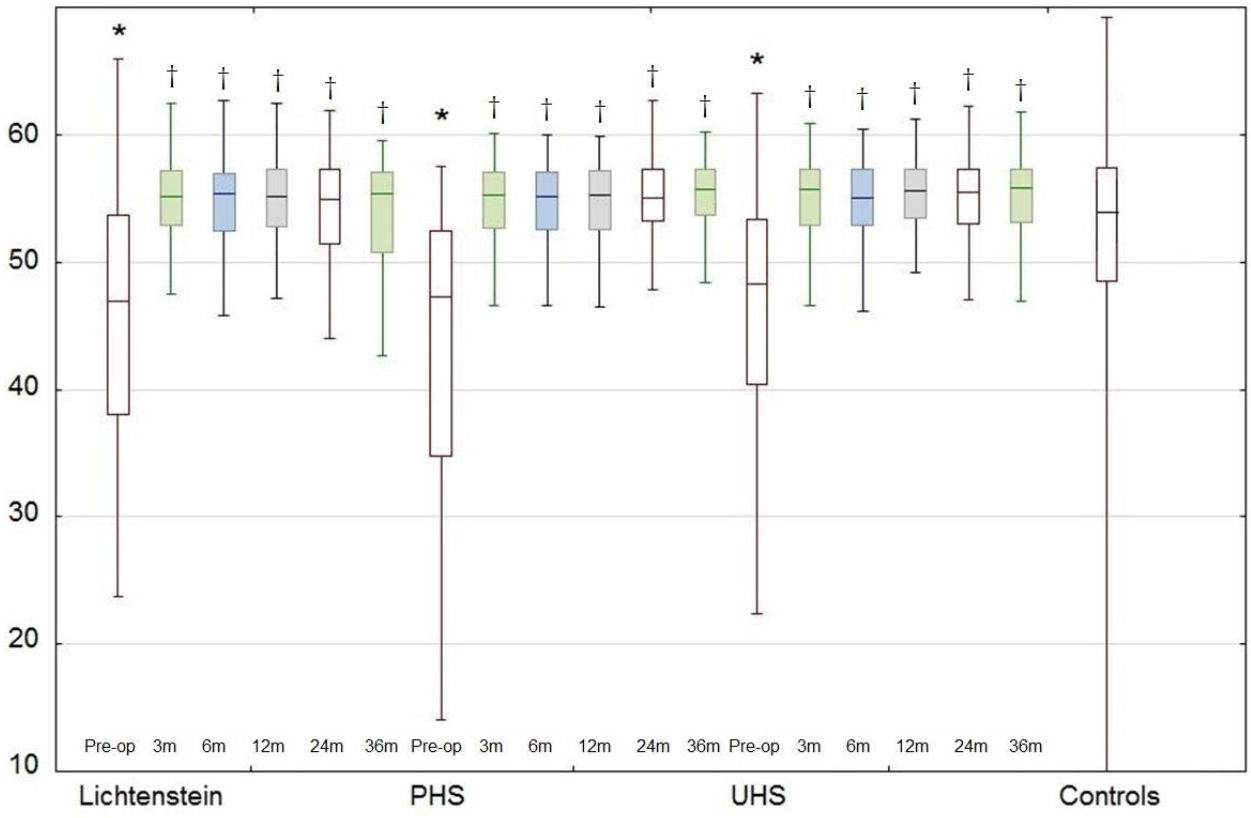

*Figure 10. Physical component score (PCS) preoperatively, 3, 6, 12, 24 and 36 months after IHR. Controls = matched controls from the normal population. Boxes represent IQR for PCS. Median and range are also given in the figure. *p<0.05 vs controls, † p<0.05 vs preoperatively.*

PAPER II AND IV

309 male patients scheduled for IHR under LA and a daycare setting were included in the study, as described in *Paper I*. Patients were followed up for a total of 36 months. Eight per cent of all patients were lost to follow-up.

Preoperatively

Prior to surgery, an inguinal bulge was present in 9 out of ten patients. Pain was the most commonly reported symptom, noted in approximately two thirds of all patients. In patients indicating pain, the score according to VAS was low, both at rest and in motion. A total of 113 patients rated their pain ≥3, according to VAS, "substantial pain". One third of all patients complained of other mild discomforting symptoms than pain such as sensations of pressure, tension, gurgles and swelling. Twenty-six per cent of all patients did not have any symptoms at all, Table 4. In all patients, three out of four physical dimensions of SF-36 were significant lower than compared to a matched control group from the normal population. Accordingly, the combined physical component score (PCS) was decreased for all patients compared to matched controls.

Patients were divided into two groups, depending on occurrence of preoperative groin pain or not. When patients were divided into those with (P, n=197) or without (N, n=112) preoperative pain, it was found that PCS in group P was significantly lower than group N, (43.5 (34.7-50.3) vs. 53.1 (47.9-55.9), $p<0.05$) as well as compared with matched controls. PCS in group N was not different from the normal population. MCS was not affected or different from the normal population before surgery in any group.

Postoperative - pain

The number of patients reporting pain was reduced from 197 to 41, $p< 0.001$, after 12 months. Thirty six of these reported pain before surgery whereas five patients developed pain after the operation. Incidence of groin pain was further reduced to 31 (12%) and 21 (7%) at 24 and 36 months after surgery, respectively. Preoperatively, pain scores according to VAS were in general low, both at rest and in motion. At 12 months after surgery, pain scores according to VAS in group P decreased significantly compared to the preoperative situation, by over 50 and 75 % at rest and in motion, respectively. Similar scores were seen in patients in group P compared to patients who

developed pain in group N at all follow-up occasions. Pain scores were unchanged during the remainder of the study period and without further changes at 24 and 36 months. At 12 months postoperatively, the number of patients with "substantial pain" was reduced to 10 patients (3 %) and declined further to a total of four patients (1.4 %) at 24 as well as 36 months after surgery.

	Pre op (n=309)			12 m (n=301)			24 m (n=254)			36 m (n=283)		
	N	**P**	**Tot**	**N**	**P**	**Tot**	**N**	**P**	**Tot**	**N**	**P**	**Tot**
	112	197	309	112 (100)	189 (96)	301 (97)	94 (84)	160 (81)	254 (82)	104 (93)	179 (90)	283 (92)
Inguinal bulge n %	101 (90)	180 (91)	281 (91)	17* (15)	38* (20)	55* (18)	11* (12)	18*§ (11)	29*§ (11)	6*§ (6)	16*§ (9)	22*§ (8)
Inguinal pain n %	0	197 (100)	197 (64)	5 (4)	36* (19)	41* (14)	5 (5)	26* (16)	31* (12)	5 (5)	16*§ (9)	21*§ (7)
VAS At rest	-	0.9 (0.3-2.5)	0.9 (0.3-2.5)	0.3 (0-1.9)	0.4* (0-2.0)	0.3* (0-2.0)	0.8 (0.4-1.2)	0.4* (0.1-1.1)	0.5* (0.3-1.2)	0.7 (0.2-1.3)	0.7* (0.2-2.3)	0.7* (0.2-2.3)
VAS In motion	-	3.3 (1.7–5.4)	3.3 (1.7–5.4)	1.6 (0.1-3.1)	0.7* (0.3-2.9)	0.7* (0.3-3.0)	1.2 (0.7-2.3)	1.0* (0.4-1.9)	1.0* (0.4-2.3)	1.4 (0.7-2)	1.4* (0.5-2.3)	1.4* (0.5-2.3)
VAS≥3	-	113 (37)	113 (37)	2 (2)	8* (4)	10* (3)	1 (1)	3* (2)	4* (2)	1 (1)	3* (2)	4* (1)
Other symptoms n %	33 (30)	70 (36)	103 (33)	19 (17)	52 (28)	71* (24)	15 (16)	41 (26)	56* (22)	15 (14)	43 (24)	58* (20)
No symptoms n %	79 (71)	0 (0)	79 (26)	88 (79)	77* (41)	189* (63)	74 (79)	93* (58)	167* (66)	84 (80)	120* (67)	204* (72)
Satisfied												
Yes n %				100 (99)	172 (94)	272 (96)	92 (99)	150 (94)	242 (96)	94 (93)	165 (97)	259 (96)
No n %				1 (1)	11 (6)	12 (4)	1 (1)	9 (6)	10 (4)	7 (7)	5 (3)	12 (4)
Missing				*11*	*6*	*17*	*1*	*1*	*2*	*3*	*9*	*12*
Recurrence n %				1 (1)	2 (1)	3 (1)	1 (1)	3 (2)	4 (2)	1 (1)	4 (2)	5 (2)

Table 4. Inguinal symptoms and distribution of VAS for pain before, 12, 24 and 36 months after IHR. (N) patients not reporting pain from their inguinal hernia before surgery, (P) patients reporting pain from their inguinal hernia before surgery, (Tot) all included patients. $p<0.05$ vs preoperatively, $^{\S}p<0.05$ vs 12 m. Values are given as median and interquartile range unless stated else.*

Other symptoms

Other discomforting symptoms than pain was frequently reported before surgery (33% of all patients). All discomforting complaints taken together were less common after IHR. By 12 months postoperatively this number was significantly reduced by 30 % (from 103 to 71). Fifty eight patients (20%) reported some discomforting symptom at 36 months and "foreign body sensation" was most common in this category, reported by 19 patients. Other discomforting symptoms were in general moderate and referred to as stiffness, itching, tingling sensations etc.

QoL

In all patients (T), three out of four physical dimensions of SF-36 were increased one year after surgery. Accordingly, PCS increased significantly in all patients (from 47 to 55) which were higher compared to controls (54). This increase was markedly higher ($p<0.05$) in patients with preoperative pain (P) (from 44 to 55) compared to patients who did not report preoperative pain (N) (from 53 to 56). However, both groups increased their score significantly. PCS remained without further differences during the study period and there were no differences between groups or matched controls at 24 or 36 months after surgery, Figure 11a. Compared to before surgery, patients with inguinal pain (P) improved their PCS significantly from 43.6 (34.7-50.3) to 55.0 (52.0-57.0), $p<0.05$ at 36 months follow-up. However, in group N, the change in PCS from 53.0 (47.9-55.9) preoperatively to 55.9 (53.7-57.3) at the end of the study, was without statistical significance.

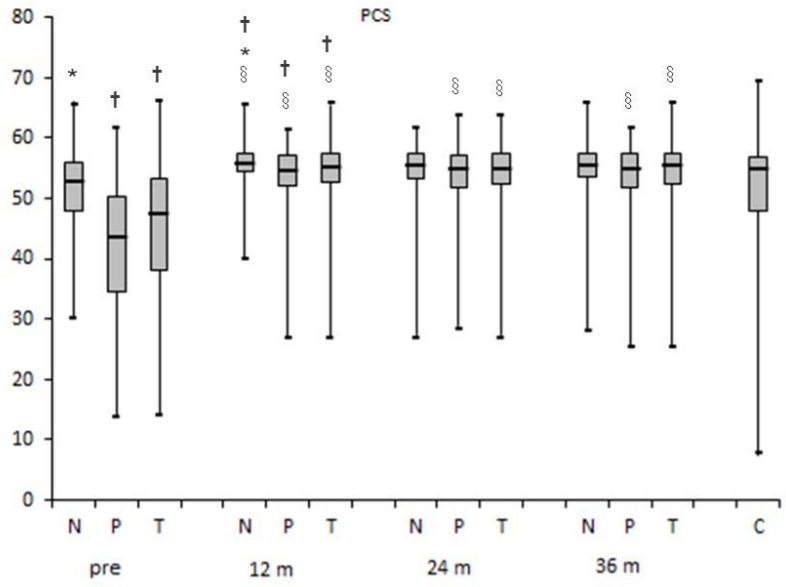

*Figure 11a. PCS before, 12, 24 and 36 months after open primary IHR. (N) patients not reporting pain from their inguinal hernia before surgery, (P) patients reporting pain from their inguinal hernia before surgery, (T) all included patients, (C) matched controls. Boxes represent IQR. Median and range are also given in the figure. * p< 0.05 vs P, † p< 0.05 vs C, § p<0.05 vs preoperatively.*

The mental component score of SF-36, MCS, was not different between groups or compared to controls before surgery. At 12 months MCS was slightly, but significant higher in groups P and T compared to controls. However, MCS was not different compared to preoperatively. There were no differences in MCS between P and N during the entire study period, Figure 11b.

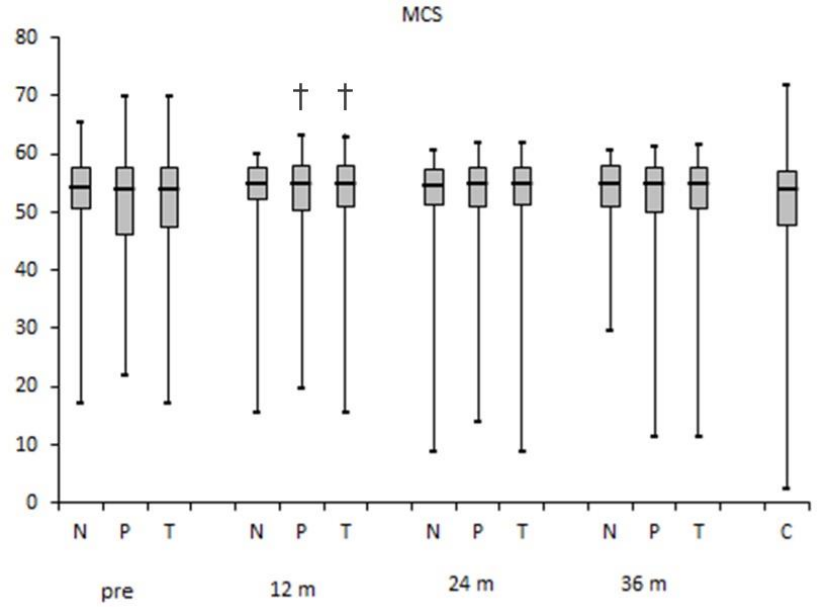

Figure 11b. MCS before, 12, 24 and 36 months after open primary IHR.
(N) patients not reporting pain from their inguinal hernia before surgery, (P) patients reporting pain from their inguinal hernia before surgery, (T) all included patients, (C) matched controls. Boxes represent IQR. Median and range are also given in the figure. † $p < 0.05$ vs C.

PAPER V

In this paper, data on male patients aged >15 years undergoing open IHR during January 1st 1999 to December 31st 2014 were collected from the Swedish Hernia Register (SHR). A total of 95 808 primary IHR with PHS (1 443) and Lichtenstein (94 365) was collected. In addition, data on all re-operations due to recurrence after a primary IHR with either of the two techniques were collected during the same time period.

At the primary operation with PHS and L, a lateral defect was most commonly reported in both groups followed by a medial hernia, together representing 9 out of 10 of all hernias. Operation time was 17 minutes shorter ($p<0.05$) and complications within 30 days were less frequent after primary repair with PHS compared to L (5.7 vs.7.6 %, $p<0.05$).

In the period January 1st 1999 to October 20th 2010 the rate of recurrent hernia repair was significantly lower in the PHS group, with a total of 24 (1.7%) vs. 2 333 (2.5%) in the Lichtenstein group, $p<0.05$. Medial defects were most common in both groups at the time of re-operation. However, the proportion of medial defects was higher after PHS (71 %) compared to 45 % after L, $p<0.05$.

The choice of surgical approach at the re-operation differed between the groups. After PHS recurrence, an open anterior mesh repair was used in a majority of all procedures (67 %) and laparoscopic (Totally extra peritoneal repair, TEP) surgery in 6 patients (25 %). In the L group, a posterior (preperitoneal) approach was used in 56 % of all re-operations; of which laparoscopic repair (either TEP or Transabdominal preperitoneal repair, TAPP) were the most commonly used techniques (38 % of all re-operations).

At re-operation, no differences in operating time were found between the groups irrespective of the re-operation was performed with open (51 vs. 63 min) or laparoscopic technique (41 vs. 50 min). However, an open repair was more time consuming than a laparoscopic operation (63 vs. 50 min, $p<0.05$) in group L, whereas this was not seen in the PHS-group (41 vs. 50 min, p= ns).

Complication rates within the first 30 days did not differ between groups after re-operation due to recurrence. However, complication rates were higher in patients re-operated for recurrence after L compared to primary IHR with the same technique (11.7 vs. 7.6, $p<0.05$) whereas this was not the case in those re-operated after primary PHS (8.3 vs. 5.7, p=ns).

DISCUSSION

PAPER I AND III

In paper I and III, the most commonly used method in open IHR, the Lichtenstein repair, was compared with two alternative methods, PHS and UHS, in a randomized controlled setting. The primary endpoint was chronic postoperative groin pain and secondary outcome perioperative course, complications, recurrence rates and changes in QoL. Potential advantages of PHS and UHS include a shortened operation time, faster recovery, reduced incidence of recurrence and degree of postoperative pain. The studies include follow-up after a short time (1 year) and medium long-term (3 years).

Based on our results, we were not able to confirm any differences between techniques regarding perioperative course in terms of operating time, intraoperative complications, postoperative pain, chronic pain, return to normal daily activities, improvement of QoL or recurrences. This suggests that all three methods can be recommended for primary IHR in LA and daycare surgery.

Earlier reports have, however, showed that the operating time is significantly shorter with PHS compared to L [63, 67, 130]. Possibly, this could be explained by the fact that the surgeons in the current study had greater experience from the L repair.

Our primary outcome was occurrence of chronic postoperative pain. Chronic pain is perhaps the most important outcome today since recurrence rates have declined to low and acceptable levels. As reported previously, pain was the most common symptom in the preoperative situation, present in almost two thirds of all patients [15, 16]. In general, pain scores postoperatively according to VAS were low and without differences between groups. Chronic pain after IHR has however, been reported in high rates varying from 0-63 % [84, 85, 131]. Although some factors are known to predispose for development of chronic inguinal pain, the underlying mechanism is not fully understood. Scarring around remaining mesh and sutures and/or nerve injuries due to surgical exploration has been suggested as potential explanations [97, 132, 133]. In theory, the different surgical technique used with PHS/UHS could, due to the design of the mesh and the technique for fixation with only a few single sutures, reduce this chronic condition. Previous reports have

suggested beneficial results regarding postoperative pain, when LW mesh was used in the Lichtenstein technique [59, 60, 134]. Therefore, a mesh made of LW material and partially resorbable components as in the UHS, could in theory further improve the results from a pain perspective.

One year after surgery, incidence of pain decreased in all groups and the degree of pain remained both at rest and in motion. There were no differences between the groups. Incidence of pain was in the same range as, or even lower than previous reports [19]. Approximately one out of three patients complained of significant pain (VAS≥ 3) before surgery and this number was reduced to three per cent one year after IHR, without differences between groups. In accordance with other studies [85, 88], the number of patients reporting pain decreased throughout the study period. Three years after surgery, a total of 21 patients (7 %) had pain, equally distributed between groups. Of these, 4 patients (1 %) reported significant pain.

Other discomforting symptoms were present in two thirds of all patients prior to surgery, without differences between the groups. These symptoms were, in general, mild. Inguinal discomfort after IHR is also common, but its significance for the patient's well-being is yet to be defined. During the study period, occurrence of discomforting symptoms was reduced, without differences between groups. Our results are comparable with earlier reports on discomfort after Lichtenstein [59, 63, 69, 86] and PHS [63, 69, 119], but there are no data available for UHS to this date.

Improvement of QoL is the ultimate goal in inguinal hernia surgery, but there are few reports comparing QoL before and after IHR. Before surgery, all three groups scored PCS similarly and significantly lower than matched controls, as reported previously [15, 77, 82]. Mental QoL (MCS) was unaffected before and after surgery and didn't differ between groups or from the normal population at any time point throughout the study. At three months after IHR, PCS was increased in all groups to levels that were not different compared with the normal population, and this improvement was sustained throughout the study period. Interestingly, improvement in PCS occurred relatively quickly after surgery and remained during the study period whereas the incidence of inguinal pain was continually reduced throughout the study period.

A total of five recurrences (1.6%) were found in the study, of which three occurred within the first 12 months after surgery, one in each group. Moreover, two more were diagnosed between 12 and 36 months postoperatively. Although our results do not indicate that one method is superior to any of the other, no conclusion can be made in terms of risk of recurrence.

PAPER II AND IV

There are surprisingly few reports in which QoL is compared before and after IHR. Obviously, to draw conclusions on the effect of IHR regarding symptoms and QoL, the preoperative situation must be considered and related to the outcome after surgery. We used the same patients included in Paper I and III, with a new design, where patients were categorized based on occurrence of preoperative pain or not.

Pain was the most commonly reported symptom in patients scheduled for IHR, present in 2/3 of all patients, and the degree was in general reported low. Symptoms, other than pain, were mild. Surprisingly, one fourth of all patients declared no symptoms at all from their hernia.

In all patients, incidence of pain was reduced by 79 % at one year after surgery. Pain scores as assessed by VAS were reduced as well. Similar to other reports [85, 88], a trend towards reduced number of patients reporting pain was noted during the study period; from 197 before surgery to 41, 31 and 21 patients (7 %) at 1, 2 and 3 years after IHR, respectively. Even though the number of patients reporting pain declined in patients with pain, the degree was relatively unchanged at this time compared to the situation at 12 months. A total of five patients from group N reported inguinal pain 3 years after surgery (24 % of all patients reporting pain). The degree of pain was rated no different compared to the 16 patients in group P who still reported pain by the end of the study. In contrast to previous reports [19], the total number of patients reporting chronic groin pain after 3 years were relatively low.

In all patients taken together (T), physical QoL according to SF-36 was impaired preoperatively compared with the normal population. Before surgery, when patients were divided depending on occurrence of pain (P) or not (N), it was found that N scored PCS significantly higher than P and

not different from controls. The difference between N and P was also present for parameters related to activities in daily life, where P scored significantly lower in a majority of all activities.

12 months after surgery, both groups improved PCS to levels that were, in fact, higher than controls and compared to the situation before surgery. The major improvement was seen in P. Also, a slight improvement in MCS was seen in P and T. This improvement was non-significant compared to preoperatively but significantly higher compared to controls. PCS and MCS did not change during the rest of the study period. At 36 months after surgery, N scored their QoL not different compared to before surgery or with controls. In P, however, the improvement in PCS remained significantly higher than preoperatively and not different from controls.

Previous studies have demonstrated that there is an association between the occurrence of groin pain before as well as after IHR and deterioration in physical QoL [15, 77-81]. This was confirmed in the current study in which patients with pain from their inguinal hernia scored physical QoL significantly lower compared with those without pain as well as with matched controls. Interestingly, at 24 as well as 36 months after IHR, the increase in physical QoL in patients with preoperative pain remained, whereas this was unchanged compared to preoperatively, and no different from controls in patients who were pain-free before surgery. Accordingly, the entire increase in QoL in all included patients during the remainder of the follow up was totally accounted for by patients who reported preoperative pain. The mental aspects of SF-36 were not as affected and MCS was not different compared to matched controls, by 24 and 36 months after surgery. This marked and sustained discrepancy in terms of improvement in QoL after IHR between patients with and without preoperative groin pain has, to the best of our knowledge, not been reported previously. With a perspective to QoL and IHR, our findings suggest that patients with pain from their inguinal hernia are those who gain the most out of IHR.

Other discomforting symptoms than pain was common before surgery, present in 33 % of all patients. The number of patients who reported such symptoms was reduced by approximately 45 % during the study period and it was the most commonly reported complaint at the end of the study, present in 58 patients (20 %) with foreign body sensation being the most commonly reported symptom. However, the significance of postoperative groin discomfort for the patient's well-being is not precisely defined and it is most often not considered a major problem. This might be illustrated

by the fact that 96 % of patients in the current study reported that they were satisfied with the outcome at 3 years after surgery and that patients with discomfort were evenly distributed between those who were and were not satisfied.

PAPER V

In paper V, the primary aims were to determine the recurrence rate after a primary IHR with PHS compared to the golden standard procedure L and to evaluate if a re-operation due to recurrence is more complicated. The basic rule in recurrent hernia repair is to use a previously untouched layer in the abdominal wall. If the primary operation was performed through an open anterior approach, the re-operation will preferably be conducted by a posterior repair, and vice versa. Our hypothesis was that a re-operation after PHS-recurrence might be more difficult, since both layers of the abdominal wall in the inguinal area already have been explored. In fact, we questioned whether a laparoscopic (preperitoneal) operation might be possible to perform in case of recurrence after PHS.

In order to include as many patients as possible, data during the period 1999 – 2014 was collected from the SHR. Data from a total of 95 808 primary IHR was collected (1 443 PHS and 94 365 L). Also, data on all 2 357 re-operations due to recurrence after primary IHR with both mentioned techniques between 1999 and 2014 was collected.

With data from one of the largest hernia registers available, we report that primary operation time was shorter and the number of complications was lower in patients undergoing repair with PHS compared with L. Also, recurrent hernia repair was significantly lower after primary PHS compared to L (1.7 vs. 2.5%, $p<0.05$). A medial defect was the most common recurrent hernia type in both groups but the proportion of medial defect was significantly higher in the PHS group. An open anterior repair was more frequently used for re-operation in the PHS-group, whereas a posterior repair was more common in the Lichtenstein group. There were no differences in operating time or number of complications at 30 days postoperatively at re-operation due to recurrence after primary IHR with PHS or L.

Robust reliable data from trials comparing surgical techniques, with recurrence as the primary endpoint is sparse. The findings of a significantly lower recurrence rate in patients operated with primary PHS repair is in corroboration with data from a retrospective series including 622 patients [68], whereas this has not been able to confirm in smaller RCTs [62, 63, 69, 70, 72, 73, 130, 135].

Any type of open anterior tension free mesh repair is used in a majority of all IHR in Sweden and L is the most common [1]. In the PHS technique, the repair is performed with an anterior and a posterior mesh as well with a plug-repair. Previous studies have suggested some advantages in primary IHR with PHS compared to L. Reported findings in favor of PHS include a shortened operating time and/or reduced postoperative pain [63, 67, 130, 136]. This was also reflected in the current study where the operation time was significantly shorter in primary PHS-repair than after L. Moreover, postoperative complication rates were lower after primary PHS-repair than after L. This is in contrast to what was reported in a meta-analysis including 1 313 patients[72], suggesting that PHS was associated with a higher complication rate compared to L.

The type of hernia defect registered in re-operation due to recurrence differed, with the proportion of medial defects being significantly higher in the PHS group. This could possibly be due to inadequate covering of the pubic tubercle since the anterior sheet is smaller than in L and single sutures are used for fixation. Some studies examining recurrence after L repair have shown that medial defects occur in more than half of the cases [137, 138] suggesting that sufficient medial covering of the mesh is crucial.

In case of re-operation for recurrence after IHR, an "untouched layer" is usually preferred and our findings support this. In recurrent hernia repair after primary PHS, an open anterior mesh technique was most frequently used (67 %) whereas a re-operation due to recurrence after L was performed with a preperitoneal repair in more than half the operations. The most common technique used after L-recurrence was TEP (33 %). Interestingly, six patients with recurrence after primary PHS were re-operated with TEP, and in none of these any postoperative complications were reported.

Operating time for surgery due to relapse did not differ between groups, either for open or laparoscopic surgery. However, conclusions could not be drawn from this as the number of patients with recurrence after PHS was so small.

Although our results might be affected by a type II error, the findings in the current study suggest that re-operation due to PHS recurrence is not more complicated compared to re-operation after L. This is also supported by the finding that complications after re-operation for L recurrence were more common than after primary operation whereas there was no corresponding difference found for PHS.

Limitations

The current study design, a retrospective cohort study, has limitations including the risk of underreporting data, incomplete data collection, lack of confounder information and possible missing information on data quality. It is also important to point out that the register contains solely data for recurrent IHR surgery and not the actual relapse incidence. However, the patients included in the analysis in this study are those in which the recurrent hernia was of sufficient clinical relevance to justify re-operation. Another weakness of our study is that the surgeon's level of competence/experience (specialist or resident) was under-reported. It could not be excluded that those who operated primary IHR with PHS as well as recurrence after the same procedure were experienced and hernia dedicated surgeons while L is a procedure that most surgeons perform, also during surgical training.

The main strengths are the large size of the cohort, that data has been collected independently and that selection bias could be minimized by the use of a complete study population on a national basis.

CONCLUSIONS

1. Lichtenstein, PHS and UHS seem to give equal and good results regarding peri- and postoperative course, complications, early recurrence, pain and QoL up to 12 months after surgery. They could therefore all be recommended for use in IHR under LA in a day care setting in male patients.

2. A large proportion of male patients scheduled for IHR might be asymptomatic. The occurrence of preoperative pain is associated with preoperative impairment as well as postoperative improvement of physical QoL. Preoperative pain is therefore an important factor to consider when scheduling a patient for IHR.

3. The satisfactory results with the use of L, PHS and UHS after IHR reported after 12 months in paper I are sustained at 3 years postoperatively. After open repair of inguinal hernia under LA, the number of patients reporting chronic pain seems to be reduced over time.

4. The relation between preoperative pain and postoperative improvement in QoL at 12 months is sustained also at long-term follow up (3 years). This underscores further that patients with preoperative pain are those who could be expected to benefit the most from IHR.

5. Re-operation due to recurrence after primary IHR with PHS is less common but not more complicated compared with after the gold standard technique; the Lichtenstein repair. A laparoscopic repair seems to be feasible for use for re-operation after PHS recurrence.

SAMMANFATTNING FÖR ICKE-KIRURGER

Ett ljumskbråck orsakas av en svaghet i ljumskens bukvägg genom vilket innehåll från bukhålan kan pressas ut, vanligtvis fett eller tarmar. Det vanligaste symptomet är smärta. Ljumskbråck drabbar ffa män och är som regel ofarligt, men kan i sällsynta fall vara livshotande. Kirurgi är den enda botande behandlingen. Operation pga ljumskbråck är det vanligaste kirurgiska ingreppet i världen. Vid operation förstärks bukväggen vanligtvis med ett nät. Ingreppet kan ofta utföras i lokalbedövning och dagkirurgi. Riskerna med operation är små och det är ovanligt att man återfår sitt bråck. Ett av det största bekymret är risken att utveckla kronisk ljumsksmärta efter operation, vilket drabbar ca 11-12 %. Det finns dock studier där mer än 50 % som opererats har dagliga ljumsksmärtor, mer än ett år efter operationen. Ett tillstånd med kronisk värk i ljumsken är starkt kopplat till försämrad livskvalitet.

Orsaken till långvarig smärta efter operation är inte helt säkerställd. Nervskador orsakade av suturer, nätmaterial och kraftig ärrbildning har föreslagits som tänkbara förklaringar. Kontinuerligt tillverkas nya nät, med nya material och ny design, i hopp om att kunna minska utvecklingen av kronisk smärta efter kirurgi. Det vanligaste använda nätet är av plast och liknar ett myggnät. Nätmassan kan ha betydelse och därför har lättviktsnät utvecklats. Utöver det vanliga platta nätet används det bl a konformade nätpluggar och dubbelbladsnät. Det finns idag drygt 160 olika nät för ljumskbråckskirurgi.

Studie I

Vid jämförelse av tre olika nätmetoder: Är det någon skillnad 12 månader efter ljumskbråcksoperation avseende operationsförlopp, återhämtning, komplikationer, återfall, smärta och livskvalitet?

309 män planerade för ljumskbråcksoperation i dagkirurgi och lokalbedövning tilldelades slumpmässigt operation med ett av tre olika nät; Lichtenstein (standardmetoden, tungviktsnät) eller ett av två olika dubbelbladsnät; Prolene Hernia System, PHS (tungviktsnät) eller UltraPro Hernia System, UHS (lättviktsnät). Patienterna följdes upp efter 14 dagar, 3, 6 och 12 månader.

Grupperna var likartade. 2/3 hade ljumsksmärtor och en försämrad livskvalitet före op som efter operationen blev normal. Alla tre grupper fick likartade goda resultat av sin ljumskbråcksoperation med få komplikationer, snabb återhämtning, måttlig smärta och förbättrad livskvalitet.

Samtliga nät kan rekommenderas för ljumskbråckskirurgi i lokalbedövning och dagkirurgi.

Studie II

Vilka symptom har män som planeras för ljumskbråcksoperation? Hur stora är besvären? Påverkar bråcket livskvaliteten? Finns det något samband mellan symptom och livskvalitet? Hur påverkas livskvalitet av operation?

Här undersöktes samma patienter som i studie 1. Patienterna delades in i två grupper beroende på förekomst av smärta eller ej före op. Patienter med smärta hade en försämrad livskvalitet jämfört med normalbefolkningen medan de smärtfria hade normala värden. Ett år efter operation hade smärtgruppen förbättrat sin livskvalitet till normal nivå och den smärtfria gruppen ökade sina värden minimalt.

Förekomst av ljumsksmärta är ett viktigt symptom att ta hänsyn till inför operation då det tydligt påverkar livskvalitet samt utfallet av en operation.

Studie III

Finns det någon skillnad 3 år efter ljumskbråcksoperation när man jämför patienter som opererats med tre olika nätmetoder, avseende livskvalitet, kronisk smärta, återfall eller andra besvärande symptom?

Studie 3 är en 3-årsuppföljning av studie 1. Uppföljning skedde efter 3, 12, 24 samt 36 månader. Inga skillnader mellan grupperna kunde påvisas vid något av de olika uppföljningstillfällena. Den förbättring i livskvalitet som sågs efter 1 år fanns kvar vid 3-årsuppföljningen. Antalet patienter med smärta minskade kontinuerligt under studietiden till ca 7 patienter/grupp (7 %), efter 3 år. Smärtan var beskedlig hos de flesta. Övriga obehagsbesvär minskade något. Fem återfall diagnostiserades, jämnt fördelat över grupperna.

Vid 3-årsuppföljning konstateras att alla tre nätmetoderna är fortsatt likvärdiga med goda resultat beträffande kronisk smärta, obehag och livskvalitet. Dessa fynd styrker ytterligare att de kan rekommenderas vid ljumskbråckskirurgi i lokalbedövning.

Studie IV

Hur påverkar en ljumskbråcksoperation livskvalitet, smärta och andra besvär på lång sikt? Finns det något samband mellan preoperativa symptom och hur en ljumskbråcksoperation påverkar livskvaliteten på lång sikt?

Tre år efter operation hade grupperna likvärdig, normal livskvalitet. Jämfört med innan operation har patienter med ljumsksmärta förbättrat sin livskvalitet till normala värden medan de smärtfria patienternas livskvalitet är oförändrad men fortfarande normal. Andelen patienter med smärta minskade drastiskt, men fem personer som inte hade smärta innan sin operation fick det efter ingreppet.

Sett ur ett livskvalitetsperspektiv så är patienter som har smärta från sitt ljumskbråck de som förbättras mest av en ljumskbråcksoperation.

Studie V

Återfall av ljumskbråck efter ljumskbråcksoperation med dubbelbladsnät: Hur vanligt är det? Vilken operationsmetod används vid operation pga återfall?
Är en återfallsoperation efter dubbelbladsnät en svårare operation jämfört med efter en standardoperation? Tar det längre tid? Är det mer komplikationer?

I den sista studien har vi jämfört dubbelbladsnät med standardmetoden (Lichtenstein).

Data från drygt 95 000 operationer erhölls från en av världens största databaser gällandes ljumskbråck, Svenskt bråckregister. Vid den första ljumskbråcksoperationen var operationstiden kortare och komplikationerna färre med dubbelnät jämfört med standardmetoden. Omoperation pga återfall var mindre vanligt efter dubbelbladsnät. Återfall efter tidigare dubbelbladsnät opererades ffa med öppen teknik medan återfall efter standardmetoden vanligast utfördes med titthålskirurgi. Operationstider och antalet komplikationer var likartade.

Ljumskbråcksoperation med dubbelbladsnät ger mindre återfall än efter standardoperationsmetoden Lichtenstein. En omoperation pga återfall efter dubbelbladsnät verkar inte vara mer komplicerad än omoperation efter standardmetoden.

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Paper I

Paper II

Paper III